Extract from Herceptin Risk Management Plan (RMP) vs13.1 highlighting updates made to RMP vs.13.0 to incorporate device performance in the RMP

NB. Please note the complete Word version of the RMP has been provided in parallel via Eudralink, and the published RMP will be provided in the closing eCTD sequence upon approval.

SECTION 7.6 EFFECT OF DEVICE FAILURE

The Herceptin subcutaneous formulation has been administered to patients, by Healthcare Professionals, using the Single-use Injection Device (SID) in clinical trials. The MAH is currently seeking approval for the SID in a Type II variation application.

The following potential for medication errors have been identified, although no adverse events associated with medication error involving the SC SID have been reported in the global safety database thus far.

- Failure to administer full dose-

If no dose is administered due to mishandling or failure of the SID, then dosing with a new SID is advised if available. Alternatively, Herceptin solution for SC injection (vial) should be administered. If there are more than one incidences of mishandling or failure of the SID, Herceptin solution for SC injection (vial) should be administered for the remainder of the treatment duration.

If a partial dose is administered, due to mishandling or failure of the SC SID, the next full dose should be administered at the next scheduled visit in 3 weeks using the SC SID.

If there are repeated incidences of mishandling or failure of the SID, then dosing with a new SC SID is advised. Alternatively, the patient can receive the Herceptin SC solution via SC injection (vial) for the remainder of the treatment duration.

Routine risk minimization activities, to reduce the likelihood of a failure to administer the full dose, include the detailed instructions provided in the SPC. In the event of a failure to administer a full dose, the SPC and PIL recommend waiting until the next scheduled dose. This information is also present in the *PIL*.

- Device performance

If the device fails to perform as expected, the HCP should return the device to the MAH. The MAH will then perform a full evaluation of the device as well as a root cause analysis. The results of these evaluations are captured in the MAH database and review of any these cases will be part of routine pharmacovigilance activities.

- Other risks associated with use of the administration system-SID

Risk minimization activities, including the clear indication of a partial delivery by the SC SID, were applied during the design of the SID and the design of the manufacturing process for Herceptin solution for injection in the SID. The measures implemented ensure that when used under the conditions and for the purposes intended, the Herceptin solution for injection in the SC SID will not compromise the clinical condition or the safety of patients or the safety and health of the user (e.g. HCP administering the drug to the patient). During device development, any risks identified to be associated with the intended use were eliminated or reduced as much as possible, while preserving the benefits offered by the SC SID. The SPC and *Instructions for Use* (*IFU*) section 7 of Patient information leaflet (PIL) contains information about the residual risks to advise the user on the safe handling of Herceptin SC solution for injection in the SC SID, including instructions to ensure correct administration of the drug.

Table 1 Description of device errors during the clinical trial programme

Product name: trastuzumab				
Description of error	Number of occurrences	Analysis of cause	Steps taken to prevent	Comment
Failure to deliver full dose	one	The SID sensed a loss of body contact. The injection mechanism stopped and the injection needle retracted automatically. Consequently, this subject received a lower dose of study drug (239.44 mg) due to human error with SID handling.	*Detailed instructions for use as well as advice for dosing in the event of device failure are included in the SPC.*	No adverse event was reported in conjunction with this medication error.

Extract from Herceptin Risk Management Plan (RMP) vs 13.2 highlighting updates made to RMP vs 13.1 to address the Rapporteurs Request for Supplementary Information

NB. Please note the complete Word version of the RMP has been provided in parallel via Eudralink, and the published RMP will be provided in the closing eCTD sequence upon approval.

SECTION 8.0 POTENTIAL FOR OFF-LABEL USE

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In an effort to quantify current off-label usage, the MAH conducted a search of the Global Safety Database cumulative through 28 October 2013. These data retrieval excluded cases of breast cancer, or gastric/oesophageal cancer (including metastatic disease) and of unknown indications. A total of 584 case reports, in which the indication for use could be ascertained, were retrieved. Of these 307 were from clinical trials (including literature cases). The safety database currently contains over 37,000 case reports on Herceptin. Therefore, the off-label case reports represent about 1.5% of all case reports for trastuzumab in the safety database.

Herceptin SC SID

The use of Herceptin SC SID is currently intended for healthcare provider (HCP) administration only. Accordingly Section 4.2 Posology and method of administration of the EU SPC states: '*Herceptin treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy (see section 4.4 of the SPC), and should be administered by a healthcare professional only*'. Similar wording is also provided in Section 3 of the PIL: '*Herceptin in administration system should only be given by a doctor or nurse.'*

Currently, no data regarding unsupervised patient self-administration with Herceptin SC SID are available. In clinical trials thus far, where patients have been able to self-administer Herceptin SC SID, each SC SID cycle was performed under the direct supervision of a HCP.

Conclusion

The phase I/II nature of the studies identified from the NCI Clinical Trials Registry and a search of the MAH's global safety database suggest that the off-label use of trastuzumab in wider clinical practice is negligible.

The MAH will continue to provide an analysis of the safety profile of trastuzumab when used with cisplatin versus oxaliplatin in gastric cancer. These analyses will be presented annually in the PBRER.

SC SID off-label use data will be presented and discussed in the RMP, once available.

SECTION 16.0 SUMMARY OF THE POST-AUTHORIZATION PHARMACOVIGILANCE DEVELOPMENT PLAN

16.1 TABLE OF ON-GOING AND PLANNED STUDIES IN THE POST-AUTHORIZATION PHARMACOVIGILANCE DEVELOPMENT PLAN

The category has been added for all studies listed in section 16.1. All studies are classified in category 3.

16.2 TABLE OF COMPLETED STUDIES FROM THE POST-AUTHORIZATION PHARMACOVIGILANCE DEVELOPMENT PLAN

The category has been added to the study listed in section 16.2. The study has been classified in category 3.

THE E.U. RISK MANAGEMENT PLAN FOR HERCEPTIN® / TRASTUZUMAB

RMP version to be assessed as part of this application:

RMP Version number: 21.0

Data lock point for this RMP: 23 May 2019

Date of final sign off:

Date and Time (UTC)	Reason for Signing	Name
18-Nov-2019 14:56:05	Deputy QPPV	[redacted]
18-Nov-2019 19:13:54	Company Signatory (PV)	

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List of Annexes **Page**

Rationale for submitting an updated risk management plan (RMP):

The Marketing Authorization Holder (MAH) proposes updating the RMP with the completed status of recently concluded Study BO29159 [MetaPHER]. A Multicenter, Open-Label, Single-Arm Safety Study of Herceptin® Subcutaneous (SC) in Combination with Perjeta® Intravenous and Docetaxel Intravenous as first line of Treatment in Patients with HER2-Positive Advanced Breast Cancer (Metastatic or Locally Recurrent).

Summary of significant changes in this RMP:

The MAH introduced the following updates to the trastuzumab RMP

- BO29159 (MetaPHER) has recently been completed. No new information obtained for the safety concern of cardiac dysfunction and Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin SC. No additional pharmacovigilance (PV) activity for the safety concern of Cardiac dysfunction and Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin SC has been conducted through this trial. Therefore, no further information from this trial will be presented in the future updates to the RMP. The final CSR for this study will be submitted to the EMA with Variation application EMEA/H/C/278/II/XXX,in November 2019 (See Part III.2)
- Cumulative patient exposure data from marketing experience have been updated in line with Periodic Benefit-Risk Evaluation Report (PBRER) 2018 (Report number 1089226) (See SV.1.2)
- Any reference to H4621g/GE28099 (MotHER Pregnancy Registry) has been removed from the RMP as MotHER Registry (H4621g/GE28099) is now closed to all patients exposed to Herceptin, P erjeta (in combination with Herceptin) or Kadcyla. No further additional PV activity will be conducted within the MotHER Registry for the safety concern of oligohydramnios (See Part III.2)
- Additional risk minimization measure of Direct Health Care Professional Communication (DHPC) for increased risk of cardiac dysfunction has been removed as additional risk minimization (See Part V.2), and therefore Annex 6 shall be not applicable
- Table 27 (Exposure to trial drug following randomization (Cohort 1 and 2, Safety population), Table 40 (Cardiac dysfunction, severity & frequency: BO22227 IV arm), Table 41 (Cardiac dysfunction, severity & frequency: BO22227 SC arm) and Table 42 (Summary of Cardiac events, special population) have been replaced with same outputs with better resolution to increase the legibility. No data for those trials have been updated

Other RMP versions under evaluation:

RMP Version number: None

Submitted on: Not applicable

Procedure number: Not applicable

Details of Currently Approved RMP:
Version number: 20.0.0

Approved with procedure: EMEA/H/C/000278/II/0147

Date of approval (opinion date): 31 October 2018

See page 1 for signature and date

[redacted] (QPPV) Date

See page 1 for signature and date

[redacted] Date

PART I: PRODUCT OVERVIEW

Active Substance(s) (INN or common name)	**Trastuzumab**
Pharmacotherapeutic group(s) (ATC Code)	**L01XC03**
Marketing Authorization Holder (or Applicant)	**Roche Registration GmbH, Germany**
Medicinal products to which this RMP refers	**One**
Invented name(s) in the European Economic Area (EEA)	**Herceptin®**
Marketing authorization procedure	**Central Authorization Procedure**
Brief description of the product including:	**Chemical Class:** Recombinant Humanized Monoclonal Antibody
	Summary of mode of action: Trastuzumab selectively targets the extracellular domain of human epidermal growth factor receptor 2 (HER2), a transmembrane tyrosine kinase receptor. Trastuzumab has been shown, both in *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.
	Important information about its composition: Trastuzumab is produced by a genetically engineered Chinese hamster ovary (CHO) cell line grown in large scale, which secretes trastuzumab into the culture medium. The antibody is then purified extensively using standard chromatographic and filtration methods.
Hyperlink to the Product Information	
Indication(s) in the EEA	**Current:** • ***Breast Cancer*** – Metastatic Breast Cancer (MBC): intravenous (IV) and subcutaneous (SC) (vial and single-use injection device [SID]). – Early Breast Cancer (EBC): IV and SC (vial and single-use injection device [SID]). • ***Metastatic Gastric Cancer (MGC)*** **:** IV only
	Proposed: Not applicable
Dosage in the EEA	**Current:**

	IV formulation:*Metastatic breast cancer* ***Three-weekly schedule*** The recommended initial loading dose of Herceptin is 8 mg/kg body weight. The recommended maintenance dose of Herceptin at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. ***Weekly schedule*** The recommended initial loading dose of Herceptin is 4 mg/kg body weight. The recommended weekly maintenance dose of Herceptin is 2 mg/kg body weight, beginning one week after the loading dose. ***Early breast cancer*** ***Three-weekly schedule*** The recommended initial loading dose of Herceptin is 8 mg/kg body weight. The recommended maintenance dose of Herceptin at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. ***Weekly schedule*** The recommended initial loading dose of Herceptin is 4 mg/kg followed by 2 mg/kg every week concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide. ***Metastatic gastric cancer*** ***Three-weekly schedule*** The recommended initial loading dose of Herceptin is 8 mg/kg body weight. The recommended maintenance dose of Herceptin at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. **Subcutaneous (SC) formulation:** The recommended dose for Herceptin subcutaneous formulation is 600 mg irrespective of the patient's body weight. No loading dose is required. This dose should be administered subcutaneously over 2-5 minutes every three weeks **Proposed:** Not applicable
Pharmaceutical form(s) and strengths	**Current:** Herceptin is available as an IV formulation (150 mg single dose vials containing powder for concentrate for solution for infusion; reconstituted concentrate contains 21 mg/mL of trastuzumab; in addition, single dose vials

	(60 mg) and multi-dose vials are available outside of the EEA). It is also available as a SC formulation (600 mg fixed-dose vial containing solution for injection which should not be reconstituted or diluted).
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the E.U.?	No

CHO=Chinese hamster ovary, EBC= Early Breast Cancer, EEA=European Economic Area, HER2=human epidermal growth factor receptor 2, IV=intravenous, MBC=Metastatic Breast Cancer, MGC=Metastatic Gastric Cancer, SC= Subcutaneous, SID = Single–Use Injection Device.

ABBREVIATIONS

Abbreviation	Definition
AC−>T	doxorubicin plus cyclophosphamide followed by docetaxel
AC−>T+H	doxorubicin plus cyclophosphamide followed by docetaxel plus trastuzumab
AC−>T−>H	doxorubicin plus cyclophosphamide followed by docetaxel followed by trastuzumab
ADA	Anti-Drug Antibodies
ADRs	Adverse Drug Reactions
ADS	Annual Data Summary
AEs	Adverse Events
ARR	administration-related reactions
CHF	Congestive Heart Failure
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DHPC	Direct Healthcare Professional Communication
DSR	Drug Safety Report
ErbB2	erythroblastic oncogene B2
EBC	Early Breast Cancer
ECHO	echocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Estrogen Receptors
E.U.	European Union
E.U.-RMP	E.U. Risk Management Plan
FDA	United States Food and Drug Administration
GC	Gastric Cancer
GVP	Good Pharmacovigilance Practice
HCP	Health Care Professional
HER-2	Human Epidermal Growth Factor Receptor-2
HLGT	High Level GroupTerms
HLT	High Level Terms
IB	Investigator’s Brochure
IBD	International Birth Date
ISR	Injection Site Reaction

IV	Intravenous
LLN	Law of Large Numbers
LVEF	left ventricular ejection fraction
MAH	Marketing Authorization Holder
MBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary of Regulatory Activities
MGC	Metastatic Gastric Cancer
MI	Myocardial Infarction
MUGA	Multigated Acquisition Scan
Nab	Neutralizing Antibody
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PAM	post-authorization measure
PBRER	Periodic Benefit Risk Evaluation Report
PFS	Progression-free survival
PR	Progesterone Receptors
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Terms
PV	Pharmacovigilance
Q1W	once a week
Q3W	every three weeks
rHuPH20	recombinant human PH20 hyaluronidase
RMP	Risk Management Plan
ROW	Rest Of World
SAEs	Serious Adverse Events
SC	Subcutaneous
SEER	Surveillance, Epidemiology, and End Results
SID	Single-use Injection Device
SmPC/SPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TAE	Targeted Adverse Event
TCH	docetaxel plus carboplatin plus trastuzumab
U.S.	United States
USPI	U.S. prescribing information

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 EARLY/METASTATIC BREAST CANCER

- Incidence

In Europe, breast cancer is the most commonly diagnosed form of cancer in women (463,800 new breast cancers in 2012 or 28.8% of total cancers reported in Europe) (Ferlay et al. 2013). There is an approximate 3-fold variation in risk among European Union (E.U.) countries; incidence rates range from 54 cases per 100,000 (Ukraine) to 147.5 cases per 100,000 (Belgium). Rates generally appear to be higher in western compared to Eastern Europe (Ferlay et al. 2013).

Globally, breast cancer is also the most common female cancer with an estimated 1.38 million cases in 2008. Worldwide, rates appear to vary by geographical region with the highest breast cancer rates in more developed, “Westernized” countries such as those in North America and Europe (Jemal et al. 2011)

It has been estimated that approximately 15%-20% of diagnosed breast cancers in women are Human Epidermal Growth Factor Receptor-2 (HER2)-positive breast cancers (Chia et al. 2008; Ross et al. 2009; Pathmanathan et al. 2012; Bilous et al. 2012)

Most breast cancers in the Western world (around 94%-95% of patients in the United States (U.S.) and Europe) are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread (Howlader et al. 2012) i.e., only around 5-6% of new cases are locally advanced (T4) or metastatic at diagnosis.

- Prevalence

The global 5-year limited duration prevalence of breast cancer is 5.2 million patients (Bray et al. 2013). The prevalence of HER2 positivity varies considerably, ranging from 9 to 74%, with an average of 22% (Chia et al. 2008). Factors that contribute to this variability include stage of disease (metastaticversus. non-metastatic), specimen type (e.g., frozen, paraffin, etc.) and assay type (e.g., fluorescence in situ hybridization [FISH], immunohistochemistry [IHC], etc.) and center (tertiary hospitals tend to report the highest rates of HER2 positivity). However most investigators tend to believe that the true range of HER2 positivity falls within the range of 15%-20% (Chia et al. 2008; Ross at al. 2009; Pathmanathan et al. 2012; Bilous et al. 2012).

- Demographics:

The incidence rate rises rapidly between 35 and 39 years of age, then levels off to a plateau after 80 years of age (Benson at al. 2009; Smigal et al. 2006).

Breast cancer is rare in men, accounting for less than 1% of all malignancies (Fentiman et al. 2006). The average age of diagnosis of breast cancer in men is 67 years.

Among patients newly diagnosed with breast cancer, 28% of those aged 20-29 years were HER2-positive, while only about 10% of those aged >75 years were HER2-positive (Clarke C,2012). Estimation of HER2-positive breast cancer in men significantly varies in the literature (5%-56%) (Onami S,2010) (Barh D,2009)**.** Although racial differences in the incidence of different breast cancer sub-types have been described (Kwan M,2009), notably for triple-negative breast cancer, no particular racial differences have been described for HER2-positive disease.

- The main existing treatment options:

Treatment of newly diagnosed, non-metastatic breast cancer:

Breast cancer is treated with a multidisciplinary approach involving surgical oncology, radiation oncology, and medical oncology, which has been associated with a reduction in breast cancer mortality. Because ductal carcinoma in situ (DCIS) and invasive breast cancer are managed differently, the discussion is restricted to invasive breast cancer. The treatment approach depends on the stage at presentation.

Non metastatic breast cancer is broadly considered in two categories:

- Early stage – includes patients with stage I, IIA, or a subset of stage IIB disease (T2N1);
- Locally advanced – includes a subset of patients with stage IIB disease (T3N0) and patients with stage IIIA to IIIC disease.

Early-stage breast cancer

Surgery is the main modality of local treatment for breast cancer, and surgery and/or radiotherapy can control loco-regional disease in the majority of patients. Conventionally, adjuvant systemic therapy is given after loco-regional therapy to eradicate micrometastatic disease and reduce the chances of distant (and local) relapse. Neoadjuvant therapy (also called 'primary systemic' or 'pre-operative' therapy) is given prior to surgery and has become a standard treatment option for many patients with newly diagnosed breast cancer. Although originally developed for patients with large and/or inoperable tumors to enable definitive surgery to be performed, neoadjuvant therapy is also now used in patients with operable EBC at high risk of recurrence (e.g., HER2+ positive tumors, node positive disease) to try to avoid a mastectomy and enable breast-conserving surgery to take place. Neoadjuvant therapy is also the primary modality of therapy for patients with inflammatory breast cancer, regardless of tumor size (Dawood et al, 2011)

Following definitive local treatment, adjuvant systemic therapy may be offered based on primary tumor characteristics, such as tumor size, grade, number of involved lymph

nodes, the status of estrogen receptors (ER) and progesterone receptors (PR), and expression of the HER2 receptor.

Tumor characteristics predict which patients are likely to benefit from specific types of therapy. For example, hormone receptor-positive patients benefit from the use of endocrine therapy. In addition, patients with HER2-positive cancers benefit from treatment using HER2-directed treatment.

For patients with early-stage breast cancer, treatment is based on tumor characteristics, patient status, and patient preferences:

- Patients with hormone receptor-positive breast cancer should receive endocrine therapy. Whether they also should receive adjuvant chemotherapy depends on patient and tumor characteristics.
- Chemotherapy is offered to patients with early-stage hormone receptor-positive cancers that have high-risk characteristics, such as high-grade tumor, large tumor size (≥2 cm), pathologically involved lymph nodes, and/or high 21-gene recurrence score (≥31).
- For patients with ER/PR and HER2-negative disease (triple-negative breast cancer), it is recommended to administer adjuvant chemotherapy if the tumor size is ≥0.5 cm. Because these patients are not candidates for endocrine therapy or treatment with HER2-directed agents, chemotherapy is their only option for adjuvant treatment, following or before radiotherapy. Patients with a triple-negative breast cancer <0.5 cm in size may forego adjuvant chemotherapy in most cases, due to minimal, if any, survival advantage.
- Patients with HER2-positive breast cancer with a tumor size >1 cm should receive a combination of chemotherapy plus HER2-directed therapy. The management of small (≤1 cm) HER2-positive breast cancers is controversial.
- Following chemotherapy, patients with ER-positive disease should also receive adjuvant endocrine therapy.

Locally advanced breast cancer

Locally advanced breast cancer is best managed with multimodality therapy employing systemic and loco-regional therapy.

Most patients with locally advanced breast cancer should receive neoadjuvant systemic therapy. The goal of treatment is to induce a tumor response before surgery and enable breast conservation. Neoadjuvant therapy results in long-term distant disease-free survival and overall survival (OS) comparable to that achieved with primary surgery followed by adjuvant systemic therapy. Selection of treatment in the neoadjuvant setting is outlined below:

- For most patients HR-positive disease, chemotherapy in the neoadjuvant setting rather than endocrine therapy is recommended. Chemotherapy is associated with higher response rates in a shorter time period. For select

patients with hormone-positive disease, neoadjuvant endocrine therapy may be an appropriate option.

- For patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, a HER2-directed agent (e.g. trastuzumab with or without pertuzumab) should be added to the chemotherapy regimen.

All patients should undergo surgery following neoadjuvant systemic therapy, even if they have a complete clinical and/or radiological response. In addition, patients who experience progression while on neoadjuvant systemic therapy should proceed with surgery, rather than switching the chemotherapy regimen.

The use of postoperative (adjuvant) systemic therapy is guided by the patient's clinical status and tumor characteristics:

- Patients who did not receive neoadjuvant systemic therapy should receive adjuvant treatment. The use of chemotherapy, biologic therapy, and/or endocrine therapy is guided by the same principles used to determine treatment for early-stage breast cancer.

For patients who received the full course of planned neoadjuvant chemotherapy

- Patients with HR-positive breast cancer should receive endocrine therapy to reduce the risk of breast cancer recurrence and breast cancer-related mortality. There is no evidence that the addition of further chemotherapy in the form of adjuvant treatment improves OS. The selection of endocrine therapy is made according to menopausal status.
- Patients with HR-negative breast cancer would typically not receive further chemotherapy in the adjuvant setting, as there is no evidence that the addition of adjuvant chemotherapy improves OS. These patients should begin post treatment surveillance.
- In some exceptional cases where the tumor progressed during neoadjuvant therapy or if the complete neoadjuvant therapy could not be delivered at the normal levels of intensity, adjuvant chemotherapy should be discussed and considered.
- Patients with HER2-positive breast cancer should receive one year of trastuzumabwith or without pertuzumab following completion of surgery without the addition of further chemotherapy.

Patients treated with neoadjuvant endocrine therapy who undergo surgery should continue endocrine therapy in the adjuvant setting. Whether or not to administer adjuvant chemotherapy should be individualized; up-to-date online article accessed 23 November 2017 [Taghian A et al.].

Although metastatic breast cancer is unlikely to be cured, meaningful improvements in survival have been seen, coincident with the introduction of newer systemic therapies. Median OS approaches two years, with a range from a few months to many years.

The selection of a therapeutic strategy depends upon both tumor biology and clinical factors, with the goal being a tailored approach. Although a subset of patients with oligometastatic disease may benefit from an intensified loco-regional approach, most patients with metastatic breast cancer receive systemic medical therapy consisting of chemotherapy, endocrine therapy, and/or biologic therapies, and supportive care measures.

Therapeutic goals: the primary goals of systemic treatment for metastatic breast cancer are prolongation of survival, alleviation of symptoms, and maintenance or improvement in quality of life, despite the toxicity associated with treatment. The median survival for metastatic breast cancer is 18 to 24 months, though this varies widely based on subtype of tumor, sites of metastatic involvement, and burden of metastatic disease, and some patients experience long-term survival.

No prospective randomized clinical trials have demonstrated that systemic therapy prolongs survival compared with best supportive care alone. However, median survival for patients with metastatic breast cancer appears to have improved over time, a trend which has been attributed to the availability of new, more effective agents, including taxanes, aromatase inhibitors, and trastuzumab. As an example, patients from the British Columbia Breast Cancer Outcomes Database who were diagnosed between 1997 and 2001 had better two-year OS than patients diagnosed between 1991 and 1995 (45 versus 34 percent).

Treatment selection is based on the following factors:

- The aim of treatment is to palliate symptoms, prolong survival, and maintain quality of life.
- Patients with visceral metastases (especially if rapidly progressing) and/or a short disease-free interval generally have an aggressive phenotype, while patients with soft tissue and bone metastases have a more indolent phenotype.
- Hormone receptor status and HER2 overexpression are important in estimating prognosis and the likelihood of response to therapy.
    - Hormone receptor (ER and/or PR) status is the major determining factor for response to endocrine therapy.
    - Likewise, HER2 overexpression is required for response to HER2-directed therapies.

Based upon these principles, selection of treatment can be individualized. Endocrine therapy is best used for patients with HR-positive breast cancer and not for patients with hormone-negative breast cancer. HER2-directed therapy is only appropriate for patients with tumors that overexpress HER2. Lastly, chemotherapy is indicated for hormone-insensitive metastatic breast cancer (i.e., patients with HR-negative breast cancer and those with HR-positive breast cancer who have become resistant to endocrine therapy). It is less clear when to use endocrine therapy versus chemotherapy as initial treatment

for patients with hormone receptor-positive metastatic breast cancer. Likewise, it is less obvious when to use single agent versus combination chemotherapy, how to best incorporate biologic therapies, and whether combined modalities are of benefit.

Treatment algorithms:

- *Hormone receptor-positive HER2-negative patients —*

In general, endocrine therapy is very likely to be beneficial for these patients, with fewer side effects compared with chemotherapy. Therefore, these should usually be used as initial treatment for patients with hormone receptor-positive disease. However, chemotherapy induces higher response rates than endocrine therapy. Therefore, patients with rapidly progressive, symptomatic disease or visceral metastases with end-organ dysfunction may be best treated with first-line chemotherapy. After chemotherapy response stabilizes (usually four to six months), a switch to maintenance endocrine therapy is a commonly employed strategy, which can reduce the treatment side effects without compromising overall survival.

Given its generally favorable toxicity profile, first-line endocrine therapy is more appropriate for most patients except those with severe symptoms or rapidly progressive visceral involvement. If the disease progresses rapidly (within a few months) following initiation of first-line endocrine therapy, chemotherapy is generally recommended as a second-line therapy rather than switching to another endocrine strategy. If time to progression on first-line endocrine therapy is greater than six months, then a switch to second-line endocrine therapy at progression is reasonable.

- *Hormone receptor-positive HER2-positive patients —*

Therapeutic options for these patients include chemotherapy, endocrine therapy, and HER2-directed therapy. HER2-directed therapy has demonstrated improved survival for patients with tumors that overexpress HER2 and thus should be part of first-line therapy for these patients.

- *Hormone receptor-negative HER2-negative patients —*

Many patients with triple- (ER-, PR-, HER2-) negative breast cancer have a particularly aggressive subtype, and first-line chemotherapy is recommended. Whether chemotherapy agents are given in combination or sequentially should be determined based on symptoms and location and burden of disease, as well as patient-related factors (i.e. preferences, goals, and overall health) up-to-date online article [Hayes DF et al.].

- Risk factors for the disease

Major risk factors for breast cancer in general include being female, older age, early menarche, late menopause, older age at first childbirth, alcohol consumption, family

history of breast cancer, postmenopausal hormone use, having benign breast disease, and being overweight/obese (Adami et al. 2002). Height is positively associated with breast cancer risk (Adami et al. 2002).

HER2 overexpression is associated with increased tumor aggressiveness, higher rates of recurrence and increased mortality in node-positive patients, while the influence in node-negative patients is more variable (Borg A,1990). Oral contraceptive use has been associated with increased risk of HER2 positive status in at least one study (Gammon et al. 1999).

- Natural history of the indicated condition in the (untreated) population:

Mortality: Breast cancer is the third leading cause of cancer death in Europe, with 131,200 new deaths reported in 2012. In the E.U., the mortality rates ranged from 16.7 per 100,000 in Spain to 29.5 per 100,000 in Belgium in 2012 (Ferlay et al. 2013). Approximately 20% of these deaths would be expected to be due to HER2-positive metastatic breast cancer, i.e., approximately 26,000 deaths in Europe and approximately 18,000 deaths in the E.U.. HER2 overexpression is independently associated with poor prognosis, indicating a more aggressive form of breast cancer, with faster relapse times at all disease stages and shortened survival (Slamon et al. 1989). Among HER2-positive metastatic breast cancer patients in the post-trastuzumab era (since 30 October 1998), the median survival is approximately 3.5 years from time of initiation of first therapy in the metastatic setting (Olson et al. 2013).

Early Breast Cancer: Survival rates for early stages of breast cancer are high (>85%). In the U.S. and Europe, almost all women diagnosed with localised disease survive for at least 5 years, compared with only about a quarter of patients diagnosed with distant metastases (Jemal et al. 2007; Sant et al. 2004).

Metastatic Breast Cancer: Metastatic disease is associated with increased tumor burden and decreased survival. According to the U.S. population-based cancer registries that constitute the Surveillance, Epidemiology, and End Results (SEER) Programme of the National Cancer Institute (NCI), stage IV breast cancer is associated with a 27-fold increase in mortality compared to stage I disease (Yancik et al. 2001).

- Important co-morbidities:

The most common conditions among breast cancer patients are: previous solid tumors, diabetes, respiratory disease, psychiatric disease, angina, obesity, myocardial infarction (MI), and stroke (Piccirillo et al. 2008).

SI.2 METASTATIC GASTRIC CANCER

- Incidence

In Europe, gastric cancer (GC) is the sixth most common cancer overall, with approximately 140,000 new cases per year (Ferlay et al. 2013). Among E.U. countries, there is an approximately 5-fold variation in risk. The highest rates, among E.U. countries, are in Belarus (42.1 cases and 17.2 cases per 100,000 for men and women, respectively) and the lowest rates are seen in Sweden (7.4 cases and 4.1 cases per 100,000 for men and women, respectively) (Ferlay et al. 2013).

Despite the historic decline in incidence and mortality, worldwide, GC is the fifth most commonly diagnosed cancer (951,000 new cases in 2012), accounting for 6.8% of total cancer cases (Ferlay et al. 2015).

HER2 is overexpressed in 10-27% of all GC cases (Vakiani 2015).

- Prevalence

The global 5-year limited duration prevalence for GC is approximately 1.7 million patients (Bray et al. 2013). Based on the MAH's knowledge, there have been no epidemiologic studies reporting on the prevalence of HER2 positive GC.

- Demographics:

Men are more likely to develop GC. Incidence rates in Europe and globally are approximately 2-fold higher in men than women (Ferlay et al. 2015).

There is a positive association with age. In a report from the population-based Munich Cancer registry, 59% of the cohort was ≥70 years old (Schlesinger-Raab et al. 2015).

High risk areas (>20 cases per 100,000) include Eastern Asia and Central and Eastern Europe (Ferlay et al. 2015). Lower rates (<10 cases per 100,000) are seen in most countries in Africa, Northern America, Australia, and New Zealand (Ferlay et al. 2015).

HER2 overexpressing cancer of the stomach or gastroesophageal junction is estimated by the MAH to be 16% of all newly diagnosed patients.

- The main existing treatment options:

To date, the only potentially curative treatment for loco-regional GC is surgery (Roth 2003). Owing to increased detection of early GC, outcomes of GC patients have improved including mortality.

For those patients and for patients with recurrent disease after surgery, the main therapeutic option is chemotherapy (Ajani 2005; Cunningham et al. 2005; National Comprehensive Cancer Network 2006).

Because advanced GC is typically not curable with current therapy, the goal of therapy in this setting is symptom palliation and to prolong progression free and overall survival while maintaining quality of life.

- Risk factors for the disease:

Demographic, environmental and lifestyle risk factors associated with increased risk of GC include socioeconomic status (Uthman et al. 2013), race/ethnicity (Dixon et al. 2014; Lui et al. 2014), smoking (Crew and Neugut 2006; Han et al. 2013), alcohol consumption (Huang et al. 2014), *Helicobacter Pylori* infection (Herrero et al. 2014), diet such as consumption of salty foods (Lin et al. 2014), and obesity .

- Natural history of the indicated condition in the untreated population:

Mortality: Gastric cancer has poor prognosis and high mortality. In Europe, mortality rates are 14.6 per 100,000 in men and 7.0 per 100,000 in women. GC is the fourth most common cause of death from cancer and accounts for approximately 6.5% of all cancer deaths in men and 5.6% of all cancer deaths in women in Europe (Ferlay J,2013) Globally, 723,000 deaths due to GC were estimated to have occurred in 2012 (Ferlay et al. 2015).

Outcome of the untreated target disease: The 5-year OS rate increased from 64% to 73% from 1986 to 2006 according to a large retrospective analysis in Korea (Suh and Yang 2015). Relative risk of mortality in GC patients in Japan has been reported as 0.52-0.72 because of increased screening (Suh and Yang 2015). However, in Western Europe and North America, GC is often diagnosed at a stage beyond resectability and survival is low. The 5-year survival in all GC patients in Europe is reported to be 24% whereas in U.S. the 5-year survival rate has been reported to be approximately 27% (Dikken et al. 2012). Regardless of their geographic region, patients with unresectable disease due to locally advanced growth or metastatic spread have a poor prognosis, with overall 5-year survival, in the range of 1%-15% (De Vivo et al. 2000; Dassen et al. 2014).

While some studies show that HER2 positive patients have poor survival (Chen et al. 2013; Liang et al. 2014; Qiu et al. 2014), many others have also reported mixed evidence on the association of HER2 status and survival in GC patients (Tanner et al. 2005; Aizawa et al. 2014; Gomez-Martin et al. 2011; He et al. 2013; Jacome et al. 2014; Lorenzon et al. 2013; Ozen et al. 2013; Yoon et al. 2012).

- Important co-morbidities:

For gastric subcardia cancers, data from Netherlands (Eindhoven Cancer Registry) suggest that the most common co-morbid conditions are cardiovascular disease, hypertension, ulcerative disease, previous cancer, diabetes, chronic obstructive pulmonary disease, cerebrovascular disease, and liver disease.

For gastric cardia cancers, data from Netherlands (Eindhoven Cancer Registry) suggest that the most common co-morbidities are cardiovascular disease, hypertension, chronic obstructive pulmonary disease, diabetes, previous cancer, cerebrovascular disease, ulcerative disease, and liver disease.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

1.1 TRASTUZUMAB IV FORMULATION

1.1.1 Toxicity

Single-Dose toxicity:

Single-dose acute toxicity studies were undertaken using intravenous bolus administration in mice and rhesus monkeys. The absence of toxicity of several different preparations and formulations of trastuzumab could be demonstrated, as measured by standard parameters like food consumption, body weight, antibody formation, clinical chemistry and macro- and microscopic examination of standard organs/tissues.

Relevance to human usage: Yes

Discussion:

This data supports the use of trastuzumab in the target population. No safety concern has been identified.

Repeated-Dose toxicity:

The repeated-dose toxicity evaluation of trastuzumab is based on a four-week study in rhesus monkeys, and 12-week and 26-week studies in cynomolgus monkeys. In all the three studies, there was a minimal toxic response, with the only noteworthy observation having been injection-site trauma in the rhesus monkey.

Relevance to human usage: Yes

Discussion:

This data supports the use of trastuzumab in the target population. No safety concern has been identified.

Reproductive toxicity:

Owing to the lack of suitability of the species conventionally used (rat or rabbit), studies were undertaken in the cynomolgus monkey at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg of trastuzumab; and no evidence has been revealed of impaired fertility. Placental transfer of trastuzumab was observed during the early and late days of gestation of the fetal development period (days 20 to 50 and days 120 to 150, respectively). Reproductive toxicity studies in female monkeys did not reveal any impaired fertility, embryo-toxicity, or effects on fetal development.

Relevance to human usage: Yes

Discussion:

The use of trastuzumab should be avoided during pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Embryofetal toxicity:

The non-clinical program revealed no direct toxicity of trastuzumab to juvenile and adult animals via the IV, SC or intrathecal route. However, when assessing the risk of reproductive toxicity to humans, it is also important to consider the significance of the rodent form of the HER2 receptor in normal embryonic development, and the embryonic death in mutant mice lacking this receptor.

Relevance to human usage: Yes

Discussion:

In the post-marketing setting, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving trastuzumab. This risk was not predicted by non-clinical IV route reproductive safety studies.

Mutagenicity:

The genotoxic potential of trastuzumab has been investigated both in vitro and in vivo. All tests gave clearly negative results. Genotoxicity testing is not required or recommended for biologics such as trastuzumab (International Conference on Harmonisation [ICH] S6(R1)). The genotoxicity assays cannot be validated for proteins as they are conducted under conditions that do not support protein stability and the proteins do not have nuclear access (in vitro or in vivo, i.e. non-genotoxic). Despite this the genotoxic potential of trastuzumab was investigated in the standard genotoxicity assays yielding negative results both in vitro and in vivo.

Relevance to human usage: Yes

Discussion:

This data supports the use of trastuzumab in humans.

1.1.2 General Safety Pharmacology

Cardiac dysfunction:

Preclinical investigations of trastuzumab associated with cardiac dysfunction, primarily on left ventricular ejection fractions and congestive heart failure (CHF), have been conducted by the MAH as well as independent investigators, and the results have suggested several possible mechanisms [De Keulenaer et al, 2010]: There may be a feedback loop involving neuregulin and erythroblastic oncogene B2 (ErbB2) (as a co-receptor) as part of a cell survival mechanism; trastuzumab may block or alter cell survival signaling; trastuzumab may down-regulate ErbB2 and thereby prevent cell survival signaling; cardiac physiological stress or damage can be exacerbated by trastuzumab; and/or there may be a direct effect of trastuzumab on cardiomyocytes.

It has been reported that HER2 signaling plays an important role in the sympathovagal control systems of the heart. In vitro studies showed that co-operation of neuregulin and the cholinergic system produced potent anti-adrenergic effects, resulting in a decrease in cardiac output and blood pressure. These findings suggest that resting sympathetic tone may be increased in patients treated with trastuzumab and in neuregulin-deficient mice [Sendur et al.2013]. However, the clinical implications of these findings, if any, have yet to be elucidated.

Relevance to human usage: Yes

Discussion:

Cardiac dysfunction has been observed in clinical trials. Cardiac dysfunction[1] is considered an important identified risk in humans

Intrathecal administration:

A small number of spontaneous cases have been received by the MAH in which it was reported that trastuzumab was administered to the patient intrathecally for the treatment of central nervous system (CNS) metastases. In response to this off-label use, the MAH has undertaken a study to investigate the safety and efficacy of intrathecal administration of trastuzumab in cynomolgus monkeys. A 4-week toxicology study with weekly intrathecal administration of trastuzumab was performed in cynomolgus monkeys at doses of 0, 3, or 15 mg, no trastuzumab-related effects on body weight, clinical signs, neurological function, clinical pathology, or anatomic pathology were noted. The applied doses and cerebral spinal fluid (CSF) concentrations achieved in the repeat dose study exceeded those reported in patients after intrathecal administration.

[1] Cardiac dysfunction was not initially identified in non-clinical studies but subsequently identified in clinical trials and subsequently re-assessed in non-clinical studies.

Relevance to human usage: Yes

Discussion:

No safety concerns were identified in relation to intrathecal administration.

1.2 TRASTUZUMAB SC FORMULATION

1.2.1 Toxicity

Repeated-Dose Toxicity:

A 13-week study was performed to confirm whether the novel route of administration and the use of the novel excipient recombinant human PH20 hyaluronidase (rHuPH20) have an effect on the safety characteristics of trastuzumab. A 30 mg/kg dose was selected to achieve systemic exposure comparable to the systemic exposure at the highest tested dose of 25 mg/kg in the 26-week IV toxicity study. The achieved exposures were comparable. No adverse Herceptin SC formulation-related effects occurred for any parameters evaluated. The study results confirmed the favorable safety profile of trastuzumab and are in line with the toxicity studies conducted with trastuzumab IV.

Relevance to human usage: Yes

Discussion:

No direct relevance other than to support the use of Herceptin SC in the target population.

Local Tolerance:

A SC local tolerance study in rabbits was performed to specifically examine the local SC tolerance of trastuzumab in a formulation containing rHuPH20. The SC formulation to be used in humans was used in the study. There were no macroscopic or microscopic findings that were attributable to treatment with Herceptin SC.

Relevance to human usage: Yes

Discussion:

Absence of local reaction in rabbits or minipigs appropriately predicted tolerability in humans.

Preclinical Safety of IV vs. SC Trastuzumab:

For the purpose of bridging between trastuzumab IV and trastuzumab SC one 13-week repeat dose toxicity study in cynomolgus monkey for trastuzumab SC containing rHuPH20 was conducted. No toxicity was noted.

In this study. a mean systemic exposure (area under the concentration-time curve [AUC]: 1-7 days) of 47,400 µg.h/mL (Day 1) to 166,000 µg.h/mL (Day 78) was achieved at the dose of 30 mg/kg. Immunogenicity of Herceptin SC was noted to be low. Only 3 samples (all from the same animal) out of a total of 36 samples taken from 4 animals from the recovery phase were positive for anti-trastuzumab antibodies (neutralizing properties were not examined). The study is considered to be a valid study to assess potential toxicity of trastuzumab SC because the animals were continually exposed to trastuzumab during the treatment period.

Relevance to human usage: Yes

Discussion
Anti-Drug Antibodies (ADAs) have been observed clinically with both IV and SC formulations. No correlation has been identified between trastuzumab ADA status and trastuzumab pharmacokinetics, efficacy, or safety. The toxicity and toxicokinetic ~~and~~ immunogenicity results from all pre-clinical toxicity studies are relevant to support further use in humans.

1.3 RHUPH20 (HYALURONIDASE)

1.3.1 Toxicity

Repeated-dose toxicity:

Results from a 39-week toxicity study of rHuPH20 administered subcutaneously in cynomolgus monkeys with a recovery phase demonstrate the absence of toxicity and limited systemic exposure to rHuPH20 upon once-weekly repeated subcutaneous administration at a dose of 2 mg/kg.

Treatment-related minimal subcutaneous perivascular lymphoplasmacytic infiltration was present at the injection site of all animals administered 2 mg/kg rHuPH20 and in 1/4 males and 1/4 females administered 0.2 mg/kg rHuPH20 sacrificed at the end of treatment. The majority of the cells were plasma cells along with a few lymphocytes. At the end of the recovery period, minimal subcutaneous perivascular lymphoplasmacytic infiltration was only present in a single male that had been administered 2 mg/kg rHuPH20, indicating substantial recovery. This result was not unexpected because subcutaneous perivascular lymphoplasmacytic infiltration is sometimes observed in cynomolgus monkeys that were injected subcutaneously with human proteins (Carbonatto et al. 2008). Consequently, this observation likely represents a nonspecific local response rather than a specific toxicity associated with rHuPH20. In view of the minimal severity of the finding and the general reaction to injection of a human protein, this finding was not considered to be adverse.

Relevance to human usage: Yes

Discussion

No direct relevance other than to support the use of rHuPH20 in the target population.

Immunogenicity to rHuPH20:

Immunogenicity in cynomolgus monkey after dosing with trastuzumab SC containing rHuPH20.

For the purpose of bridging between trastuzumab IV and trastuzumab SC one 13-week repeat dose toxicity study in cynomolgus monkey for trastuzumab SC containing rHuPH20 was conducted. No toxicity was noted.

Immunogenicity of rHuPH20: Following subcutaneous injections in the 13-week trastuzumab SC containing rHuPH20 study in cynomolgus monkey, seven out of 20 animals were considered positive for anti-rHuPH20 antibodies and the antibodies had neutralizing activity. However, neutralizing antibodies to rHuPH20 had no effect on the subcutaneous dispersion of the injection solution. Immunogenicity in cynomolgus monkey after dosing with rHuPH20 alone.

Cynomolgus monkey and human PH20 hyaluronidases are 89% homologous. This difference caused an immune reaction in cynomolgus monkeys toward rHuPH20. In the pivotal 39-week toxicity study in cynomolgus monkey, the reduction in hyaluronidase activity in plasma specimens following chronic repeated doses of 2 mg/kg was consistent with an increase in hyaluronidase neutralizing activity (neutralizing titre). Both total anti-rHuPH20 antibody (ADA) titre and neutralizing titre response correlated with dose and generally increased over time. These results were not unexpected because repeat administration of a human protein in cynomolgus monkeys can lead to an immunogenic response. After the 4-week recovery period, titres dropped by approximately 50% from peak levels. The presence of neutralizing activity was not correlated with adverse effects.

Relevance to human usage: Yes

Discussion:

Antibodies to rHuPH20 have been observed in humans. No correlation has been identified between trastuzumab ADA status and trastuzumab pharmacokinetics, efficacy, or safety. 'Immunogenicity/ Hypersensitivity and Anaphylaxis of Herceptin SC' is considered as important potential risk in humans

Embryo-fetal toxicity in mice after treatment with rHuPH20:

Reproductive toxicology studies in mice with rHuPH20 revealed embryo-fetotoxicity at doses ≥ 9 mg/kg/day, and did not show teratogenic potential. This effect is considered to be related to the achieved high systemic exposure to rHuPH20 in mice and may have been related to disruption or degradation of hyaluronan in the developing embryos. rHuPH20 is a highly purified recombinant form of the naturally occurring human hyaluronidase enzyme. The enzyme breaks down hyaluronan which is an important glycosaminoglycan component of the cardiac jelly, critical for the formation of the heart during embryogenesis. Studies in hyaluronan synthase deficient mice (Camenish et al. 2000) and studies in whole embryos (Baldwin et al. 1994) in which hyaluronan was degraded and demonstrated the importance of hyaluronan during a specific time period in normal heart development.

Due to the low doses (<0.0025 mg/kg) of rHuPH20 in patients via trastuzumab SC, no systemic exposure was detected (m5-3-1 BP22023). The doses applied in mice were significantly higher (approximately 95-fold) than the doses in humans.

There is no clinical or scientific evidence of teratogenic effects in over 60 years of experience with animal derived hyaluronidase in humans.

Relevance to human usage: Yes

Discussion:

High systemic exposure to rHuPH20 in pregnant women via inadvertent IV administration of the SC formulation may lead to possible spontaneous abortion, stillbirth, or fetal growth restriction.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Due to the different designs of the pivotal studies (monotherapy versus. combination therapy, different comparators, different disease settings, different data collection, etc.) no pooled analyses were performed.

Clinical trials exposure is presented below by indication and by race, age, and sex, where appropriate. In Studies BO16348 (HERA) and BO18255 (ToGA), for Asian race, "Oriental" was used, and in the other studies, "Asian".

SIII.1 METASTATIC BREAST CANCER

SIII.1.1 Study H0648g

Table 1 Study H0648g Duration of Exposure

HER2−Positive Breast Cancer (H0648g)				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Herceptin + AC	143	8.6 (0.4)	1–27	8.3
AC Alone	138	7.3 (0.4)	1–27	7.1
Herceptin + Paclitaxel	92	8.0 (0.5)	0–22	7.6
Paclitaxel Alone	96	4.6 (0.3)	0–13	4.0
Total	469	7.3 (0.2)	0–27	7.1

AC = Anthracycline + cyclophosphamide.

Source: Biostatistics([redacted])
pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_race_caucasian) Database (FINAL)

Table 2 Study H0648g Duration of Exposure by Age Group

HER2−Positive Breast Cancer (H0648g)								
	Persons		Person Time (months) Mean (SE)		Range (months)		Median	
Age Group	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65
Herceptin + AC	124	19	8.9 (0.4)	6.8 (0.9)	1−27	2−16	8.7	6.7
AC Alone	117	21	7.5 (0.4)	6.3 (0.9)	1−27	1−16	7.3	6.4
Herceptin + Paclitaxel	81	11	8.1 (0.5)	7.2 (1.5)	0−22	0−14	7.6	6.9
Paclitaxel Alone	84	12	4.6 (0.3)	4.5 (0.8)	0−13	1−10	4.0	4.8
Total	406	63	7.4 (0.2)	6.3 (0.5)	0−27	0−16	7.3	5.5

AC = Anthracycline + cyclophosphamide.

Source: Biostatistics([redacted])
pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_age_18to65)
Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_age_above65)
Database (FINAL)

Table 3 Study H0648g Duration of Exposure by Race

HER2−Positive Breast Cancer (H0648g)				
Race	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Herceptin + AC				
Caucasian	127	8.7 (0.4)	1−27	8.5
Asian	1	6.2 (N/A)	6−6	6.2
Black	10	8.4 (1.5)	2−19	8.2
Other	5	6.7 (1.6)	2−12	7.3
AC Alone				
Caucasian	124	7.1 (0.4)	1−27	6.6
Asian	2	7.0 (1.7)	5−9	7.0
Black	6	8.4 (0.6)	6−10	8.1
Other	6	10.5 (2.8)	3−23	9.4
Herceptin + Paclitaxel				
Caucasian	83	8.0 (0.5)	0−22	7.6
Asian	3	7.8 (1.6)	5−10	8.5
Black	2	4.7 (2.3)	2−7	4.7
Other	4	8.3 (1.3)	5−10	8.9
Paclitaxel Alone				
Caucasian	86	4.6 (0.3)	0−13	4.0
Asian	1	3.9 (N/A)	4−4	3.9
Black	3	8.0 (3.0)	3−13	7.5
Other	6	3.5 (0.7)	2−6	3.3

AC = Anthracycline + cyclophosphamide, N/A= not applicable..

Source: Biostatistics([redacted]) pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_race_caucasian) Database (FINAL)

Source: Biostatistics([redacted]) pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_race_asian) Database (FINAL)

Source: Biostatistics([redacted]) pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_race_black) Database (FINAL)

Source: Biostatistics([redacted]) pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_race_other) Database (FINAL)

SIII.1.2 Study H0649g

Table 4 Study H0649g Duration of Exposure

HER2−Positive Breast Cancer (H0649g)				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Total	222	4.8 (0.3)	0–24	3.0

Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety) Database (FINAL)

Table 5 Study H0649g Duration of Exposure by Age Group

HER2−Positive Breast Cancer (H0649g)				
Age Group	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
≥18 to ≤65	198	4.8 (0.3)	0–24	3.0
>65	24	4.6 (0.7)	1–14	4.0

Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety_age_18to65) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety_age_above65) Database (FINAL)

Table 6 Study H0649g Duration of Exposure by Race

HER2−Positive Breast Cancer (H0649g)				
Race	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Caucasian	188	4.8 (0.3)	0–24	3.0
Asian	9	7.6 (1.9)	1–14	6.4
Black	9	2.0 (0.3)	1–3	2.1
Other	16	4.2 (1.4)	1–17	2.3

Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety_race_caucasian) Database (FINAL)
Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety_race_asian) Database (FINAL)
Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety_race_black) Database (FINAL)
Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety_race_other) Database (FINAL)

SIII.1.3 Study M77001

Table 7 Study M77001 Duration of Exposure

HER2−Positive MBC(M77001)				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Taxotere Alone	94	6.5 (0.4)	1–35	6
Taxotere plus Herceptin	92	12.2 (1.0)	1–43	10
Total	186	9.3 (0.6)	1–43	7

Table 8 Study M77001 Duration of Exposure by Age Group

HER2−Positive MBC (M77001)								
	Persons		Person Time (months) Mean (SE)		Range (months)		Median	
Age Group	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65
Taxotere Alone	83	11	6.5 (0.5)	6.2 (0.5)	1−35	3−8	6	6
Taxotere + Herceptin	83	9	12.3 (1.0)	11.2 (2.7)	1−43	3−25	10	7
Total	166	20	9.4 (0.6)	8.5 (1.3)	1−43	3−25	7	6

Table 9 Study M77001 Duration of Exposure by Race

HER2−Positive MBC (M77001)				
Race	Persons	Person Time (months) Mean (SE)	Range (months)	Median
Taxotere Alone				
White	85	6.6 (0.5)	1–35	6
Black/African American	4	5.6 (0.5)	5–7	5
American Indian/Alaska Native	1	4.8	5–5	5
Other	4	4.8 (1.2)	1–7	6
Taxotere + Herceptin				
White	91	12.2 (1.0)	1–43	10
Black/African American	1	13.5	13–13	13
American Indian/Alaska Native	-	-	-	-
Other	-	-	-	-

SIII.1.4 Study BO16216 (TANDEM)

Table 10 Study BO16216 (TANDEM) Duration of Exposure

HER2−Positive MBC (BO16216)				
	Persons	Person Time (months) Mean (SE)	Range (months)	Median
AnastrazoleAlone	104	6.7 (0.8)	1–63	3
Anastrazole plus Herceptin	103	13.5 (1.7)	2–72	6
Total	207	10.1 (1.0)	1 – 72	5

Table 11 Study BO16216 (TANDEM) Duration of Exposure by Age Group

HER2−Positive MBC (M77001)								
	Persons		Person Time (months) Mean (SE)		Range (months)		Median	
Age Group	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65
AnastrazoleAlone	83	21	7.0 (1.0)	5.7 (1.1)	2−63	1−21	4	3
Anastrazole plus Herceptin	80	23	14.6 (2.0)	9.7 (2.4)	2−72	3−46	7	5
Total	163	44	10.7 (1.1)	7.8 (1.4)	2−72	1−46	5	4

Table 12 Study BO16216 (TANDEM) Duration of Exposure by Race

HER2−Positive MBC (M77001)				
Race	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Anastrazole Alone				
White	73	7.5 (1.1)	1–63	4
Black/African American	1	2.9 (N/A)	3–3	3
American Indian/Alaska Native	13	3.3 (0.4)	2–7	3
Asian	9	4.5 (0.9)	2–11	3
Other	8	7.5 (1.7)	2–16	7
Anastrazole plus Herceptin				
White	82	15.1 (2.0)	2–72	7
Black/African American	1	3.5 (N/A)	4–4	4
American Indian/Alaska Native	6	12.3 (5.8)	3–39	6
Asian	6	6.4 (2.3)	2–15	3
Other	8	5.1 (1.2)	2–10	3

SIII.2 EARLY BREAST CANCER

SIII.2.1 Study BCIRG 006 (H2296s)/GO00773

Table 13 Study BCIRG 006 (H2296s)/GO00773 Duration of Exposure

HER2−PositiveEBC: BCIRG 006 (H2296s)/GO00773				
Study arm	**Duration of exposure (months)**			
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
AC→T	1041	5.8 (0.0)	1–9	5.9
AC→TH	1077	14.5 (0.2)	1–71	15.5
TCH	1056	12.4 (0.1)	1–79	12.8
Total	3174	11.0 (0.1)	1–79	12.7

AC→T = doxorubicin + cyclophosphamide followed by docetaxel;
AC→TH = doxorubicin + cyclophosphamide followed by docetaxel + Herceptin;
TCH = docetaxel + carboplatin + Herceptin

Source: Biostatistics([redacted])
pgm(/immuno/her2/bcirg006/rmp201309/programs/t_dur_safety) output (t_safety)
Database (FINAL).

Table 14 Study BCIRG 006 (H2296s)/GO00773 Duration of Exposure by Age Group

HER2−PositiveEBC: BCIRG 006 (H2296s)/ GO00773								
	Persons		Person Time (months) Mean (SE)		Range (months)		Median	
Age Group	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65
AC→T	988	53	5.8 (0.0)	5.6 (0.1)	1−9	2−7	5.9	5.8
AC→TH	1033	44	14.5 (0.2)	13.6 (0.8)	1−71	3−34	15.5	15.5
TCH	1000	56	12.4 (0.1)	11.8 (0.5)	1−79	1−23	12.8	12.7
Total	3021	153	11.0 (0.1)	10.2 (0.4)	1−79	1−34	12.7	11.5

AC→T=doxorubicin + cyclophosphamide followed by docetaxel;
AC→TH=doxorubicin + cyclophosphamide followed by docetaxel + Herceptin;
TCH=docetaxel + carboplatin + Herceptin.Source: Biostatistics([redacted])
pgm(/immuno/her2/bcirg006/rmp201309/programs/t_dur_safety) output
(t_safety_age_18to65)Database (FINAL)Source: Biostatistics([redacted])
pgm(/immuno/her2/bcirg006/rmp201309/programs/t_dur_safety) output
(t_safety_age_above65)
Database (FINAL)

SIII.2.2 Study B-31/N9831 – Joint Analysis[1]

Table 15 Study B-31/N9831 – Joint Analysis Duration of Exposure

Adjuvant Treatment of HER2−Positive EBC (B-31/N9831 – Joint Analysis)				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
AC−>T	1655	6.4 (0.0)	0–11	6.2
AC−>T+H	2000	14.6 (0.1)	3–21	14.9
AC−>T−>H	364	20.2 (0.3)	6–33	20.7
Total	4019	11.4 (0.1)	0–33	9.3

AC−>T = doxorubicin plus cyclophosphamide followed by docetaxel;
AC−>T+H = doxorubicin plus cyclophosphamide followed by docetaxel plus Herceptin;
AC−>T−>H = doxorubicin plus cyclophosphamide followed by docetaxel followed by Herceptin.

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety) Database (FINAL)

[1] Data taken from the 8-year median follow-up report.

Table 16 Study B-31/N9831 – Joint Analysis Duration of Exposure by Age Group

Adjuvant Treatment of HER2−Positive EBC (B-31/N9831 – Joint Analysis)								
	Persons		Person Time (months) Mean (SE)		Range (months)		Median	
Age Group	≥18 to ≤ 65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65
AC−>T	1551	104	6.4 (0.0)	5.9 (0.2)	0−11	0−9	6.2	5.8
AC−>T+H	1863	137	14.7 (0.1)	14.2 (0.3)	3−21	4−20	14.9	14.8
AC−>T−>H	346	18	20.3 (0.3)	19.7 (1.0)	6−33	14−24	20.7	19.9
Total	3760	259	11.5 (0.1)	11.1 (0.4)	0−33	0−24	9.3	9.1

AC−>T = doxorubicin plus cyclophosphamide followed by docetaxel;
AC−>T+H = doxorubicin plus cyclophosphamide followed by docetaxel plus Herceptin;
AC−>T−>H = doxorubicin plus cyclophosphamide followed by docetaxel followed by Herceptin.

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_age_18to65) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_age_above65)
Database (FINAL)

Table 17 Study B-31/N9831-Joint Analysis Duration of Exposure by Race

Adjuvant Treatment of Early HER2−Positive Breast Cancer (B-31/N9831 – Joint Analysis)				
Race	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
AC−>T				
White	1358	6.4 (0.1)	0–11	6.1
Asian	47	5.9 (0.4)	0–9	5.8
Black	142	6.5 (0.2)	0–9	7.5
Hawaiian	16	7.1 (0.3)	5–9	7.9
Hispanic	72	6.6 (0.3)	0–11	7.9
Indian	4	4.7 (0.9)	2–6	5.3
Other	10	6.6 (0.6)	2–8	7.2
Unknown	6	5.8 (0.9)	2–8	5.7
AC−>T+H				
White	1682	14.7 (0.1)	3–21	14.9
Asian	68	14.0 (0.5)	5–19	14.8
Black	131	14.2 (0.4)	3–20	14.9
Hawaiian	12	16.8 (0.7)	12–20	17.6
Hispanic	75	14.2 (0.4)	6–19	15.0
Indian	6	14.3 (1.2)	9–18	14.8
Other	15	14.7 (1.0)	7–18	15.2
Unknown	11	13.5 (1.4)	4–18	14.5
AC−>T−>H				
White	313	20.4 (0.3)	6–33	20.7
Asian	11	19.1 (1.0)	15–23	18.4
Black	22	19.3 (1.2)	12–26	21.7
Hawaiian	1	23.1 ()	23–23	23.1
Hispanic	12	21.7 (1.8)	14–31	23.7
Indian	1	15.0 (N/A)	15–15	15.0
Other	4	17.4 (0.6)	16–18	17.5
Unknown	0	0	0	0
Total				
White	3353	11.5 (0.1)	0–33	10.2
Asian	126	11.2 (0.5)	0–23	10.7

Table 17 Study B-31/N9831-Joint Analysis Duration of Exposure by Race (cont.)

Black	295	10.8 (0.3)	0–26	8.4
Hawaiian	29	11.7 (1.0)	5–23	8.6
Hispanic	159	11.1 (0.4)	0–31	8.8
Indian	11	10.9 (1.6)	2–18	14.6
Other	29	12.3 (1.0)	2–18	14.6
Unknown	17	10.8 (1.3)	2–18	12.6

AC−>T = doxorubicin plus cyclophosphamide followed by docetaxel;
AC−>T+H = doxorubicin plus cyclophosphamide followed by docetaxel plus Herceptin;
AC−>T−>H = doxorubicin plus cyclophosphamide followed by docetaxel followed by Herceptin.

N/A= not applicable

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_white) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_asian) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_black) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_hawaiin) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_hispanic) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_indian) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_other) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_unknown) Database (FINAL)

SIII.2.3 Study BO16348 (HERA)*

Table 18 Study BO16348 (HERA) Duration of Exposure

Adjuvant Treatment of HER2−Positive Breast Cancer (BO16348 [HERA])				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Observation Only	1744	18.9 (0.2)	0–25	24
Herceptin 1 Year	1682	23.0 (0.1)	1–25	25
Herceptin 2 Year	1673	23.2 (0.1)	1–30	25
Remain in Observation	379	24.9 (0.0)	18–25	25
New Herceptin	896	14.8 (0.2)	1–26	13
Total	6374	20.9 (0.1)	0–30	25

*Data taken from the 8-year median follow-up report.

Table 19 Study BO16348 (HERA) Duration of Exposure by Age Group

Adjuvant Treatment of HER2−Positive Breast Cancer (BO16348 (HERA))								
	Persons		**Person Time (months)** Mean (SE)		**Range** (months)		Median	
Age Group	**≥18 to ≤65**	**>65**	**≥18 to ≤65**	**>65**	**≥18 to ≤65**	**>65**	**≥18 to ≤65**	**>65**
Observation Only	1642	102	18.8 (0.2)	19.7 (0.7)	0–25	0−25	23	25
Herceptin 1 Year	1588	94	23.1 (0.1)	22.0 (0.7)	1–25	1−25	25	25
Herceptin 2 Year	1583	90	23.3 (0.1)	22.1 (0.7)	1–30	1−26	25	25
Remain in Observation	341	38	24.9 (0.0)	24.9 (0.0)	18–25	24−25	25	25
New Herceptin	862	34	14.8 (0.2)	15.1 (1.1)	1–26	1−25	13	13
Total	6016	358	20.9 (0.1)	21.0 (0.4)	0–30	0−26	25	25

Table 20 Study BO16348 (HERA) Duration of Exposure by Race

Adjuvant Treatment of HER2−Positive Breast Cancer (BO16348 (HERA))				
Race	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Observation Only				
Other	273	19.4 (0.5)	0–25	25
White	1453	18.8 (0.2)	0–25	23
Oriental	7	20.8 (1.9)	13–25	24
American Indian/ Alaska Native	-	-	-	-
Black/ African American	6	16.8 (4.0)	1–25	19
Multiple	2	14.0 (11)	3–25	14
Native Hawaiian/ Other Pacific Islander	2	21.0 (3.9)	17–25	21
Unknown	1	24.9	25–25	25
Herceptin 1 Year				
Other	262	23.3 (0.3)	1–25	25
White	1404	23.0 (0.1)	1–25	25
Oriental	6	24.9 (0.0)	25–25	25
American Indian/ Alaska Native	1	12.6	13–13	13
Black/ African American	8	24.9 (0.0)	25–25	25
Multiple	1	24.9	25–25	25
Native Hawaiian/ Other Pacific Islander	-	-	-	-

Table 20 Study BO16348 (HERA) Duration of Exposure by Race (cont.)

Unknown	-	-	-	-
Herceptin 2 Year				
Other	264	23.0 (0.3)	1–27	25
White	1397	23.3 (0.1)	1–30	25
Oriental	5	23.4 (1.5)	18–25	25
American Indian/ Alaska Native	1	24.9	25–25	25
Black/ African American	5	24.9 (0.0)	25–25	25
Multiple	-	-	-	-
Native Hawaiian/ Other Pacific Islander	1	24.9	25–25	25
Unknown	-	-	-	-
Remain in Observation				
Other	58	24.9 (0.0)	25–25	25
White	317	24.8 (0.0)	18–25	25
Oriental	-	-	-	-
American Indian/ Alaska Native	-	-	-	-
Black/ African American	2	24.9 (0.0)	25–25	25
Multiple	1	24.9	25–25	25
Native Hawaiian/ Other Pacific Islander	1	24.9	25–25	25
Unknown	-	-	-	-
New Herceptin				
Oriental	5	22.2 (2.4)	13–25	24
Other	147	15.4 (0.5)	1–25	13
White	741	14.7 (0.2)	1–26	13

Table 20 Study BO16348 (HERA) Duration of Exposure by Race (cont.)

American Indian/ Alaska Native	-	-	-	-
Black/ African American	1	24.4	24–24	24
Multiple	-	-	-	-
Native Hawaiian/ Other Pacific Islander	1	12.8	13–13	13
Unknown	1	12.7	13–13	13
Total				
Other	1004	21.1 (0.2)	0–27	25
White	5312	20.9 (0.1)	0–30	25
Oriental	23	22.7 (0.9)	13–25	25
American Indian/ Alaska Native	2	18.7 (6.2)	13–25	19
Black/ African American	22	22.7 (1.3)	1–25	25
Multiple	4	19.5 (5.5)	3–25	25
Native Hawaiian/ Other Pacific Islander	5	20.9 (2.5)	13–25	25
Unknown	2	18.8 (6.1)	13–25	19

SIII.2.4 Study BO22227 (HannaH)

Table 21 Study BO22227 (HannaH) Duration of Exposure*

HER2−Positive Breast Cancer (BO22227 HannaH)				
	Persons	**Person Time (months) Mean**	**Range (months)**	**Median**
Herceptin IV	298	12.2	1.0–15.2	12.8
Herceptin SC (vial)	297	12.2	1.0–15.2	12.8
Total	595	12.2	1.0–15.2	12.8

*Data taken from updated Clinical Study Report with data cut off of 9 July 2012

Table 22 Study BO22227 (HannaH) Duration of Exposure by Age

HER2−Positive Breast Cancer (BO22227 HannaH)								
	Persons		Person Time (months) Mean (SD)		Range (months)		Median	
Age Group	>18 to ≤65	≥65	>18 to ≤ 65	≥65	>18 to ≤65	≥65	>18 to ≤65	≥65
Herceptin IV	275	23	12.2 (2.6)	11.7 (3.2)	1.0– 15.2	2.3– 14.2	12.8	12.7
Herceptin SC (vial)	264	33	12.2 (2.6)	12.0 (2.6)	1.0– 15.2	3.7– 14.1	12.8	12.7
Total	539	56	12.2 (2.6)	11.9 (2.8)	1.0– 15.2	2.3– 14.2	12.8	12.7

Duration of Safety Observation is calculated from date of first study treatment to 28 days after last dose of treatment

Program : $PROD/cd10326o/j22227o/stdmdursa.sas Output $PROD/cd10326o/j22227o/reports/stdmdursa_SAF.lst 27SEP2013 17:

Table 23 Study BO22227 (HannaH) Duration (in Months) of Exposure by Race

	Trastuzumab IV (N=298)	Trastuzumab SC	Total (N=595)
American Indian or Alaska Native n	3	3	6
Mean	11.0	10.7	10.9
SD	4.38	4.26	3.87
Median	13.1	13.1	13.1
Q1-Q3	6.0-14.0	5.8-13.2	6.0-13.2
Asian n	61	64	125
Mean	12.2	12.3	12.2
SD	2.07	2.26	2.16
Median	12.7	12.8	12.7
Q1-Q3	12.6-12.9	12.7-13.1	12.6-13.0
Black Or African American n	6	10	16
Mean	13.4	11.4	12.2
SD	0.24	3.28	2.72
Median	13.3	12.8	13.2
Q1-Q3	13.2-13.4	10.3-13.8	12.7-13.6
OTHER n	20	20	40
Mean	12.3	12.5	12.4
SD	2.56	0.90	1.89
Median	12.7	12.8	12.7
Q1-Q3	12.7-13.3	12.7-13.0	12.7-13.2
White n	208	200	408
Mean	12.1	12.1	12.1
SD	2.77	2.76	2.76
Median	12.8	12.9	12.8
Q1-Q3	12.7-13.2	12.7-13.2	12.7-13.2
Min-Max	1.0-15.2	1.0-15.2	1.0-15.2

Duration of Safety Observation is calculated from date of first study treatment to 28 days after last dose of treatment

Program : $PROD/cd10326o/j22227o/stdmdursr.sas

Output : $PROD/cd10326o/j22227o/reports/stdmdursr_SAF.lst

27SEP2013 17:10 Page 1 of 1

SIII.2.5 Study MO16432 (NOAH)

Table 24 Study MO16432 (NOAH) Duration of Exposure

Neoadjuvant–Adjuvant HER2–Positive Breast Cancer (MO16432)				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Herceptin with or without Chemotherapy (HER2+)	115	12.5 (0.2)	2–25	13
Chemotherapy Alone (HER2+)	113	10.1 (0.5)	2–26	8
Chemotherapy Alone (HER2–)	99	7.5 (0.1)	1–9	8
Total	327	10.2 (0.2)	1–26	8

HER2 = Human Epidermal Growth Factor Receptor 2

Table 25 Study MO16432 (NOAH) Duration of Exposure by Age

Neoadjuvant−Adjuvant HER2−Positive Breast Cancer (MO16432)								
	Persons		Person Time (months) Mean (SD)		Range (months)		Median	
Age Group	>18 to ≤65	≥65	>18 to ≤65	≥65	>18 to ≤65	≥65	>18 to ≤65	≥65
Herceptin with or without Chemotherapy (HER2+)	106	8	12.4 (0.2)	13.5 (1.1)	2–25	8−19	13	13
Chemotherapy Alone (HER2+)	97	16	9.9 (0.6)	11.4 (1.5)	2–26	8−23	8	8
Chemotherapy Alone (HER2−)	88	11	7.6 (0.1)	6.8 (0.6)	1–9	2−8	8	8
Total	291	35	10.1 (0.2)	10.5 (0.9)	1–26	2−23	8	8

HER2 = Human Epidermal Growth Factor Receptor 2

Table 26 Study MO16432 (NOAH) Duration of Exposure by Race

Neoadjuvant–Adjuvant HER2–Positive Breast Cancer (MO16432)				
Race	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Herceptin with or without Chemotherapy (HER2+)				
White	115	12.5 (0.2)	2–25	13
Chemotherapy Alone (HER2+)				
White	113	10.1 (0.5)	2–26	8
Chemotherapy Alone (HER2–)				
White	99	7.5 (0.1)	1–9	8
Total				
White	327	10.2 (0.2)	1–26	8

HER2 = Human Epidermal Growth Factor Receptor 2.

SIII.2.6 Study MO22982 (PrefHER)

Table 27 Exposure to Trial Drug following randomization (Cohorts 1 and 2; Safety Population)

Cohort 1	SC SID Period (N=242)	IV Period (N=241)	IV Continuation (N=226)	SID Self-Admin (N=43)	Overall (N=244)
Number of Cycles					
n	242	241	226	43	244
Mean (SD)	3.9 (0.45)	4.0 (0.27)	5.5 (2.63)	2.3 (0.67)	13.3 (3.43)
Median	4.0	4.0	5.0	2.0	13.0
25th, 75th percentile	4.0, 4.0	4.0, 4.0	3.0, 7.0	2.0, 3.0	11.0, 16.0
Min, Max	1, 4	1, 4	1, 10	1, 4	1, 18
Total Number of Cycles (n (%))					
1	5 (2.1)	1 (0.4)	4 (1.8)	3 (7.0)	1 (0.4)
2	1 (0.4)	2 (0.8)	25 (11.1)	27 (62.8)	0 (0.0)
3	1 (0.4)	1 (0.4)	31 (13.7)	11 (25.6)	2 (0.8)
4	235 (97.1)	237 (98.3)	32 (14.2)	2 (4.7)	2 (0.8)
5	0 (0.0)	0 (0.0)	39 (17.3)	0 (0.0)	3 (1.2)
6	0 (0.0)	0 (0.0)	20 (8.8)	0 (0.0)	2 (0.8)
Total Number of Cycles (n (%))					
7	0 (0.0)	0 (0.0)	25 (11.1)	0 (0.0)	0 (0.0)
8	0 (0.0)	0 (0.0)	11 (4.9)	0 (0.0)	5 (2.0)
9	0 (0.0)	0 (0.0)	4 (1.8)	0 (0.0)	2 (0.8)
10	0 (0.0)	0 (0.0)	35 (15.5)	0 (0.0)	27 (11.1)
11	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	28 (11.5)
12	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	31 (12.7)
13	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	36 (14.8)
14	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (9.0)
15	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	20 (8.2)
16	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.0)
17	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.9)
18	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	51 (20.9)

Roche: MO22982/CIL-TS/FINAL/EXP01P.SAS
Produced: 16 March 2016, 11:20
Source: Listing 16.2.5.1.1
Notes: [1] Percentages are based on the number of patients in the respective group.
Source: Abridged by PDRD from mainoutput Adapted from Table 14.1.13.1 *EXP01P*

Table 27 Exposure to Trial Drug following randomization (Cohorts 1 and 2; Safety Population) (cont.)

Cohort 2	SC Vial Period (N=237)	IV Period (N=237)	IV Continuation (N=10)	SC Vial Cont. (N=208)	Overall (N=239)
Number of Cycles					
n	237	237	10	208	239
Mean (SD)	3.9 (0.54)	3.9 (0.31)	3.4 (1.96)	5.5 (2.93)	12.7 (3.64)
Median	4.0	4.0	3.0	5.0	13.0
25th, 75th percentile	4.0, 4.0	4.0, 4.0	2.0, 4.0	3.0, 8.0	10.0, 15.0
Min, Max	1, 5	1, 4	1, 7	1, 10	1, 18
Total Number of Cycles (n (%))					
1	7 (3.0)	2 (0.8)	2 (20.0)	19 (9.1)	3 (1.3)
2	1 (0.4)	0 (0.0)	1 (10.0)	19 (9.1)	0 (0.0)
3	2 (0.8)	6 (2.5)	3 (30.0)	21 (10.1)	1 (0.4)
4	226 (95.4)	229 (96.6)	2 (20.0)	23 (11.1)	0 (0.0)
5	1 (0.4)	0 (0.0)	0 (0.0)	30 (14.4)	4 (1.7)
6	0 (0.0)	0 (0.0)	1 (10.0)	20 (9.6)	1 (0.4)
Total Number of Cycles (n (%))					
7	0 (0.0)	0 (0.0)	1 (10.0)	21 (10.1)	7 (2.9)
8	0 (0.0)	0 (0.0)	0 (0.0)	10 (4.8)	11 (4.6)
9	0 (0.0)	0 (0.0)	0 (0.0)	7 (3.4)	17 (7.1)
10	0 (0.0)	0 (0.0)	0 (0.0)	38 (18.3)	19 (7.9)
11	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (8.8)
12	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	25 (10.5)
13	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	32 (13.4)
14	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (8.8)
15	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (9.2)
16	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (4.2)
17	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.9)
18	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (15.9)

Roche: MO22982/CIL-TS/FINAL/EXP01P.SAS
Produced: 16 March 2016, 11:20
Source: Listing 16.2.5.1.1
Notes: [1] Percentages are based on the number of patients in the respective group.
Source: Abridged by PDRD from mainoutput,Adapted from Table 14.1.13.1 EXP01P

SIII.2.7 Study MO28048 (SafeHER)

Cohort A (SC vial): Planned/enrolled/treated: 1800/1867/1864: Study treatment: Manual SC injection presentation: Herceptin SC 600 mg/5 mL vial containing a ready to use solution with a nominal content of 600 mg of Herceptin.

Cohort B Single-use Injection Device (SID): Planned/enrolled/treated: 700/710/709: Study treatment: Device presentation: Herceptin SC 600 mg/5 mL pre-filled SID. The cartridge included in the device contains a nominal content 600 mg of Herceptin.

Table 28 Study MO28048 (SafeHER): Number of Cycles Administered: Safety Population

Table 14.1.13.1 Study Drug Exposure – Number of Cycles
(Safety Population)

	Cohort A (N=1864)	Cohort B (N=709)	Cohort B (Selfadmin) (N=550)	Overall (N=2573)
Number of Cycles				
n	31681	12246	7614	43927
Mean (SD)	17.0 (3.38)	17.3 (2.88)	13.8 (4.29)	17.1 (3.25)
Median	18.0	18.0	16.0	18.0
Min, Max	1, 19	1, 18	1, 17	1, 19
Total Number of Cycles (n (%))				
1	18 (1.0)	6 (0.8)	15 (2.7)	24 (0.9)
2	10 (0.5)	3 (0.4)	7 (1.3)	13 (0.5)
3	9 (0.5)	1 (0.1)	6 (1.1)	10 (0.4)
4	23 (1.2)	5 (0.7)	9 (1.6)	28 (1.1)
5	14 (0.8)	4 (0.6)	7 (1.3)	18 (0.7)
6	9 (0.5)	1 (0.1)	9 (1.6)	10 (0.4)
7	13 (0.7)	6 (0.8)	12 (2.2)	19 (0.7)
8	16 (0.9)	2 (0.3)	12 (2.2)	18 (0.7)
9	4 (0.2)	4 (0.6)	10 (1.8)	8 (0.3)
10	5 (0.3)	1 (0.1)	8 (1.5)	6 (0.2)
11	8 (0.4)	2 (0.3)	19 (3.5)	10 (0.4)
12	17 (0.9)	6 (0.8)	14 (2.5)	23 (0.9)
13	4 (0.2)	0	27 (4.9)	4 (0.2)
14	9 (0.5)	4 (0.6)	38 (6.9)	13 (0.5)
15	9 (0.5)	3 (0.4)	59 (10.7)	12 (0.5)
16	11 (0.6)	2 (0.3)	119 (21.6)	13 (0.5)
17	19 (1.0)	8 (1.1)	179 (32.5)	27 (1.0)
18	1663 (89.2)	651 (91.8)	0	2314 (89.9)
19	3 (0.2)	0	0	3 (0.1)

Roche: M028048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/EXP0XP.SAS
Produced: 17 August 2015, 5:57
Source: Listing 16.2.5.1.1 and 16.2.5.1.2
Notes: [1] Percentages are based on the number of patients in the respective group
[2] Total number of cycles includes the cycles with missing and delayed doses

Table 29 Study MO28048 (SafeHER) :Demographics: Safety Population

Table 14.1.4.1 Demographics
(Safety Population)

	Cohort A (N=1864)		Cohort B (N=709)		Overall (N=2573)	
Race (n (%))						
White	1421	(76.2)	556	(78.4)	1977	(76.8)
Black	25	(1.3)	6	(0.8)	31	(1.2)
Asian	295	(15.8)	83	(11.7)	378	(14.7)
Other	65	(3.5)	24	(3.4)	89	(3.5)
N/A (per local regulations)	50	(2.7)	39	(5.5)	89	(3.5)
Unknown	8	(0.4)	1	(0.1)	9	(0.3)
Ethnicity (n (%))						
Hispanic or Latino	366	(19.6)	129	(18.2)	495	(19.2)
Chinese	78	(4.2)	8	(1.1)	86	(3.3)
Indian (Indian subcontinent)	36	(1.9)	22	(3.1)	58	(2.3)
Japanese	1	(0.1)	1	(0.1)	2	(0.1)
Mixed	22	(1.2)	15	(2.1)	37	(1.4)
Other	1307	(70.1)	511	(72.1)	1818	(70.7)
Unknown	54	(2.9)	23	(3.2)	77	(3.0)
Gender (n (%))						
Male	4	(0.2)	0		4	(0.2)
Female	1860	(99.8)	709	(100.0)	2569	(99.8)

Roche: MO28048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/DEM0XP.SAS
Produced: 17 August 2015, 5:50
Source: Listing 16.2.4.1
Notes: [1] Percentages are based on the number of patients in the respective group
[2] Weight categories are based on overall safety population

Table 29 Demographics: Safety Population (cont.)

Table 14.1.4.1 Demographics
(Safety Population)

	Cohort A (N=1864)	Cohort B (N=709)	Overall (N=2573)
Age (years)			
n	1864	709	2573
Mean (SD)	54.0 (12.01)	53.0 (11.33)	53.7 (11.83)
Median	54.0	52.0	53.0
Min, Max	20, 88	27, 83	20, 88
Unknown	0	0	0
Age category (n (%))			
<75 years	1768 (94.8)	686 (96.8)	2454 (95.4)
>=75 years	96 (5.2)	23 (3.2)	119 (4.6)
Height (cm)			
n	1848	694	2542
Mean (SD)	160.9 (7.48)	161.7 (7.13)	161.1 (7.39)
Median	161.0	162.0	161.0
Min, Max	140, 186	131, 182	131, 186
Unknown	16	15	31
Weight (kg)			
n	1861	705	2566
Mean (SD)	68.64 (14.272)	68.76 (14.168)	68.67 (14.241)
Median	67.00	67.00	67.00
Min, Max	33.6, 144.0	39.0, 150.0	33.6, 150.0
Unknown	3	4	7

Roche: M028048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/DEM0XP.SAS
Produced: 17 August 2015, 5:50
Source: Listing 16.2.4.1
Notes: [1] Percentages are based on the number of patients in the respective group
[2] Weight categories are based on overall safety population

Table 29 Demographics: Safety Population (cont.)

Table 14.1.4.1 Demographics
(Safety Population)

	Cohort A (N=1864)		Cohort B (N=709)		Overall (N=2573)	
Weight categories						
(<45kg)	31	(1.7)	9	(1.3)	40	(1.6)
P10 (<=53.0 kg)	226	(12.1)	68	(9.6)	294	(11.4)
Q1 (<=59.0 kg)	501	(26.9)	176	(24.8)	677	(26.3)
Q2 (>59.0 kg:<=67.0 kg)	454	(24.4)	187	(26.4)	641	(24.9)
Q3 (>67.0 kg:<=77.0 kg)	442	(23.7)	183	(25.8)	625	(24.3)
Q4 (>77.0 kg)	464	(24.9)	159	(22.4)	623	(24.2)
Unknown	3	(0.2)	4	(0.6)	7	(0.3)
Region						
Western Europe	992	(53.2)	440	(62.1)	1432	(55.7)
Eastern Europe	293	(15.7)	98	(13.8)	391	(15.2)
Africa	62	(3.3)	12	(1.7)	74	(2.9)
Asia Pacific	324	(17.4)	96	(13.5)	420	(16.3)
Americas	193	(10.4)	63	(8.9)	256	(9.9)

Roche: M028048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/DEM0XP.SAS
Produced: 17 August 2015, 5:50

Source: Listing 16.2.4.1
Notes: [1] Percentages are based on the number of patients in the respective group
[2] Weight categories are based on overall safety population

SIII.3 HER2 POSITIVE GASTRIC CANCER

SIII.3.1 Study BO18255 (ToGA)

Table 30 Study BO18255 (ToGA) Duration of Exposure

HER2−Positive Advanced Gastric Cancer (BO18255 (ToGA))				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Fluoropyrimidine/ Cisplatin	290	8.3 (0.3)	0–31	8.9
Herceptin/ Fluoropyrimidine/ Cisplatin	294	11.7 (0.5)	1–48	10.5
Total	584	10.0 (0.3)	0–48	9.9

Table 31 Study BO18255 (ToGA) Duration of Exposure by Age

HER2−Positive Advanced Gastric Cancer (BO18255 (ToGA))								
	Persons		**Person Time (months) Mean (SD)**		**Range (months)**		**Median**	
Age Group	**>18 to ≤65**	**≥65**	**>18 to ≤65**	**≥65**	**>18 to ≤65**	**≥65**	**>18 to ≤65**	**≥65**
Fluoropyrimidine/ Cisplatin	206	84	8.5 (0.3)	8.0 (0.5)	0–31	1−29	8.9	8.8
Herceptin/ Fluoropyrimidine/ Cisplatin	202	92	11.8 (0.5)	11.6 (0.8)	1–48	1−45	10.6	10.1
Total	408	176	10.1 (0.3)	9.9 (0.5)	0–48	1−45	10.0	9.4

Source: Biostatistics([redacted]) pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_age_18to65)Database (FINAL)

Source: Biostatistics([redacted]) pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_age_above65) Database (FINAL)

Table 32 Study BO18255 (ToGA) Duration of Exposure by Race

HER2−Positive Advanced Gastric Cancer (BO18255 (ToGA))				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Fluoropyrimidine/ Cisplatin				
Oriental	158	9.3 (0.4)	1–31	10.0
Caucasian	105	7.4 (0.3)	1–17	7.6
Black	2	8.2 (1.7)	7–10	8.2
Other	25	5.9 (0.8)	0–15	6.1
Herceptin/ Fluoropyrimidine/ Cisplatin				
Oriental	151	12.2 (0.6)	1–46	11.2
Caucasian	115	11.3 (0.7)	1–48	10.2
Black	1	8.2 (N/A)	8–8	8.2
Other	27	11.1 (1.5)	1–30	8.8
Total				
Oriental	309	10.7 (0.4)	1–46	10.2
Caucasian	220	9.4 (0.4)	1–48	9.0
Black	3	8.2 (1.0)	7–10	8.2
Other	52	8.6 (0.9)	0–30	6.6

Source: Biostatistics([redacted])
pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_race_black) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_race_other) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_race_caucasian) Database (FINAL)

Table 33 Study BO18255 (ToGA) Duration of Exposure by Sex

HER2−Positive Advanced Gastric Cancer (BO18255 (ToGA))								
	Persons		Person Time (months) Mean (SD)		Range (months)		Median	
Gender	Male	Female	Male	Female	Male	Female	Male	Female
Fluoropyrimidine/ Cisplatin	218	72	8.2 (0.3)	8.7 (0.5)	0–31	1−26	8.8	9.1
Herceptin/ Fluoropyrimidine/ Cisplatin	226	68	12.1 (0.5)	10.5 (0.9)	1–48	1−39	10.6	9.7
Total	444	140	10.2 (0.3)	9.6 (0.5)	0–48	1−39	10.0	9.2

Source: Biostatistics([redacted]) pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_sex_male) Database (FINAL)

Source: Biostatistics([redacted]) pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_sex_female) Database (FINAL)

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 34 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Hypersensitivity	Treatment with trastuzumab is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients[a]	No	Hypersensitivity is contraindicated in E.U.-SmPC.
Severe dyspnea	Treatment with trastuzumab is contraindicated in patients with severe[b] dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy	No	Severe dyspnea is contraindicated in E.U.-SmPC.
Serious cardiac illness or medical conditions Serious cardiac illness or medical conditions including history of or existing (CHF), history of myocardial infarction (MI), other cardiomyopathy, poorly controlled hypertension, uncontrolled arrhythmia	Heart failure has been observed in patients receiving Herceptin therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline containing chemotherapy.	No	In Section 4.4 of the E.U. SmPC Special warnings and precautions of use, treatment of patients with these pre-existing conditions with Herceptin is not recommended. Cardiac dysfunction is classified as important identified risk in humans (see SVII. 3 and SVIII).
Low Left Ventricular Ejection Fraction (LVEF) Patients with low left ventricular ejection fraction (<50% or <55%, depending on the patient	Patients are thought to be at increased risk of cardiac toxicity associated with Herceptin administration	No	LVEF <55% included in Section 4.4 Special Warnings and Precautions for Use, E.U. SmPC. Cardiac dysfunction is classified as important identified risk in humans (see

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
population)			SVII. 3 and SVIII).
Pregnant or lactating women Women of childbearing potential or less than one year after menopause (unless surgically sterile) who are unable or unwilling to use adequate contraceptive measures during study treatment	At the design stage of the initial pivotal trials in the MBC setting, it was not known whether Herceptin can affect reproductive capacity or cause harm to the fetus. Reproduction studies in cynomolgus monkeys observed placental transfer of Herceptin during the early and late fetal development period. In the post marketing setting cases of fetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus have been reported in pregnant women receiving Herceptin. Therefore women of childbearing potential should use effective contraception during treatment with Herceptin and for at least 7 months after treatment has been concluded. Pregnant women should not be treated with Herceptin. It is not known whether Herceptin is secreted in human milk. As human immunoglobulin G (IgG) is secreted in human milk, and the potential for absorption and harm to the infant is unknown,	No	Prevention of pregnancy by using adequate contraceptive measures during Herceptin treatment is considered appropriate. Section 4.6 (Fertility, pregnancy, and lactation) of the current E.U. SmPC adequately covers this information.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
	women should not breast feed during Herceptin therapy and for 7 months after the last dose.		
Clinically significant infections	Patients may not be able to tolerate myelosuppressive chemotherapy and are at increased risk of infectious complications associated with myelosuppression.	No	No specific warning or exclusion included in the E.U. SmPC since assessment of patients' fitness for chemotherapy is part of routine oncology practice.
Evidence of Central Nervous System (CNS) metastases	Patients were excluded due to concerns that monoclonal antibodies like trastuzumab cross the blood brain barrier poorly and such patients also tend to have aggressive disease and may have insufficient time to benefit from treatment in a trial setting	No	This exclusion criterion was not related to the safety of the patient population
Life expectancy less than 3 months	In clinical trials, patients with short life expectancy are usually excluded.	No	This exclusion criterion was not related to the safety of the patient population. Not applicable for Herceptin use outside of clinical trials
Current significant or uncontrolled gastrointestinal (GI) bleeding	Patients with gastrointestinal (GI) bleeding may not be able to comply with study assessments as GI bleeding is often a symptom of progression of disease. Further to this, these patients may not tolerate myelosuppressive chemotherapy. Serious adverse events (SAEs) with GI bleeding	No	No specific warning or exclusion included in the E.U. SmPC since assessment of patient's fitness for chemotherapy is part of routine oncology practice.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
	and gastric perforation have been reported in patients treated with Herceptin.		
Active infection with HIV, HBV or HCV	Patients may not be able to tolerate myelosuppressive chemotherapy and are at increased risk of infectious complications associated with myelosuppression.	No	No specific warning or exclusion included in the E.U. SmPC since assessment of patient's fitness for chemotherapy is part of routine oncology practice. This concern is not considered by the MAH to be a sufficient reason to limit physician, options in treatment of patients with active infections with trastuzumab.

AE=Adverse events, CHF=congestive heart failure, CNS=Central Nervous System, E.U.-SmPC=European Summary of Product Characteristics, GI=gastrointestinal, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IgG= Immunoglobulin G; LVEF= left ventricular ejection fraction, MI=Myocardial infarction, SAE=Serious Adverse Events

[a] Includes rHuPH20 as excipient in SC formulation

[b] E.U. SmPC

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAM

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Adverse events with long latency (up to 10 years) considered related by the reporter can be identified:

Patients treated with Herceptin IV in clinical trials have been followed up for 10 years in Study BCIRG 006 (H2296s)/GO00773 and for 11 years in BO16348 (HERA) study.

Long-term safety of Herceptin SC 5 year follow-up is now complete in Study BO22227 (HannaH) and is ongoing forMO28048 (SafeHER) trial. In the Study BO22227 (HannaH), the overall safety profile of Herceptin SC was consistent with the known safety profile for Herceptin IV. No new safety signals were observed, and similar incidences of cardiac adverse events (AEs) were observed in the lower weight patient quartiles in the Herceptin SC treatment arm compared with the corresponding group in the Herceptin IV treatment arm.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 35 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of special population	Exposure
Pregnant women	Not included in clinical development program
Breastfeeding women	Not included in clinical development program
Patients with relevant comorbidities:	
Patients with hepatic impairment	Not included in clinical development program
Patients with renal impairment	Not included in clinical development program
Patient with cardiovascular impairment	Not included in clinical development program
Patients with respiratory impairment	Not included in clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable
Immuno-compromised patients	Not included in clinical development program

Type of special population	Exposure
Population with relevant different ethnic origin	There were no restrictions to study enrolment regarding race and ethnicity; however, based on higher incidence of breast cancer in the western world, fewer patients from the Asian region were included in breast cancer (BC) trials compared to Caucasian patients. However, this is reversed in the MGC/ metastatic gastroesophageal junction (MGEJC) indication due to the higher incidence of gastric cancer (GC) in Asia
Subpopulations carrying known and relevant genetic polymorphisms	Not applicable
Other:	
Male Patients	*Metastatic GC/GEJ cancer:* BO18255 (ToGA) = 594 patients BO27798 (HELOISE) = 296 patients *Breast Cancer:* Male patients were usually excluded from the Herceptin breast cancer program as male breast cancer is a rare disease accounting for <1% of all male tumours.
Children	Not included in clinical development program
Elderly	1188 patients. Refer to Module SIII for study wise details on elderly patient exposure.

BC=Breast Cancer; GC=Gastric cancer; GEJ=Gastroesophageal junction; MGC=Metastatic gastric cancer; MGEJ=Metastatic Gastroesophageal junction

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

SV.1.1.1 Worldwide Exposure from Marketing Experience (Excluding the United States and Japan)

The estimation of the market exposure to Herceptin cumulatively (from 25 September 1998 [International Birth Date (IBD)] until 30 September 2018) was done based on the number of vials sold and average dose per patient over the course of treatment.

The assumptions for calculation of European Economic Area (EEA) and Rest of World (ROW) patient exposure along with demographic breakdowns are provided as follows:

- The patient exposure data in the EEA assumes 64% of Herceptin IV volume is for use in patients with (EBC, 30% is for use in the MBC setting, and 6% is for use in the metastatic gastric setting. For Herceptin SC, 83% is for use in patients with EBC and 17% is for use in the MBC setting.
- The patient exposure data in RoW assumes 72% of Herceptin IV volume is for use in patients with EBC, 26% is for use in the MBC setting, and 2% is for use in the metastatic gastric setting. For Herceptin SC, 89% is for use in patients with EBC and 11% is for use in the MBC setting.
- The duration of treatment is 349 days in the EBC setting and 365 days in the MBC setting Herceptin in first line MBC is mainly used with pertuzumab with a treatment longer than in all the other lines). In the MGC setting, the duration of treatment is 189 days.

SV.1.1.2 Cumulative Patient Exposure from Marketing Experience in the United States

The assumptions for calculation of U.S. patient exposure along with demographic breakdowns are as follows:

- The patient exposure data presented are based on a patient model that assumes 74% of U.S. sales is for use in patients with EBC, 22% of sales is for use in the MBC setting, and 4% of sales is for use in the MGC setting. Patient exposure is calculated from actual vials sold divided by vials per patient estimates from the patient model.
- According to data obtained via patient tracking activities, approximately 20% of patients receiving Herceptin for EBC, 33% of patients receiving Herceptin for MBC, and 41% of patients receiving Herceptin for MGC in the United States are 65 years or older.
- Patient tracking data also suggests that 14% of patients are receiving Herceptin weekly, 66% of patients are receiving Herceptin on a 3-weekly regimen and 20% receive it on another dosing schedule (primarily once a week [Q1W] to Q3W).
- Epidemiology data indicates 0.8% of patients with breast cancer are male, and 68% of gastric cancer patients are male. Overall, approximately 7% of Herceptin patients are male.

- The vial size changed in the United States during the time interval. The MAH started selling Herceptin in 150-mg vials in May 2017. Therefore, the MAH reports separate patient numbers exposed to the two vial sizes during the time interval.
- HER2-positive breast cancer or gastric cancer is extremely rare in patients <18 years old. Therefore, estimated pediatric exposures in the United States are not available.

SV.1.2 Exposure

The cumulative marketing exposure by region is presented in Table 36.

The cumulative and interval market exposure to Herceptin was estimated based on the number of vials sold and average dose per patient over the course of treatment. The volume sold by Roche is sourced from Roche supply chain and financial systems (Controlling Profitability Analysis). The sales data are provided on a monthly basis; therefore, the exposure is available from the IBD to the point nearest the data lock point (DLP) of the 2018 Periodic Benefit-Risk Evaluation Report (PBRER) report number 1089226 (i.e., 30 September 2018).

Since the IBD, an estimated cumulative total of 2.9 million patients have received Herceptin from marketing experience. An estimated 2,754,709 patients have received Herceptin for breast cancer and 160,879 patients have received Herceptin for MGC. For all regions, the exposure in breast cancer can be further broken down into exposure in EBC and MBC (1,519,236 patients and 1,043,454 patients, respectively).

Table 36 Cumulative Patient Exposure from Marketing Experience by Region

	Region			
Indication	**Worldwide excluding the United States and Japan**	**United States**	**Japan**	**Total**
EBC	1,026,904	459,018	33,314	1,519,236
MBC	712,819	305,877	24,758	1,043,454
EBC or MBC[a]	21,064	—	170,955	192,019
Total BC	**1,760,787**	**764,895**	**229,027**	**2,754,709**
MGC	75,924	46,064	38,891	160,879
Total	**1,836,711**	**810,959**	**267,918**	**2,915,588**

BC=breast cancer; EBC=early breast cancer; MBC=metastatic breast cancer; MGC=metastatic gastric cancer.
Note: Rounding errors may be introduced in the total figure.
[a] Exposure via the Patient Access Program is included.

The cumulative marketing exposure by formulation is presented in Table 37. An estimated 2,678,934 patients have received the IV formulation of Herceptin. An

estimated 185,740 patients have received the SC formulation of Herceptin (600 mg solution for injection in vial). Of these patients, 149,142 patients have been treated for EBC and 36,598 patients have been treated for MBC.

The cumulative marketing exposure by dose and dosing regimen is presented in Table 38. Dose is unknown for most of these patients and estimates have only been available for the U.S. market based on the regimen for the IV formulation only. In the United States, the Q3W regimen has been used more frequently than the Q1W regimen.

Table 37 Cumulative Patient Exposure from Marketing Experience by Formulation

Indication	Herceptin Formulation		
	Intravenous	Subcutaneous	Unknown
EBC	1,348,091	149,142	22,002
MBC	989,958	36,598	16,898
EBC or MBC [a]	192,019	—	—
Total BC	**2,530,067**	**185,740**	**38,900**
MGC	148,866	—	12,013
Total	**2,678,934**	**185,740**	**50,913**

BC=breast cancer; EBC=early breast cancer; MBC=metastatic breast cancer; MGC=metastatic gastric cancer. Note: Rounding errors may be introduced in the total figure.

[a] Exposure via the Patient Access Program is included.

Table 38 Cumulative Exposure from Marketing Experience by Dose and Dosing Regimen

Indication	Dose for Herceptin IV and SC Formulations (mg)					Dosing Regimen of Herceptin IV Formulation [a] (U.S. only)		
	60	150	440	600	Unknown	Q1W	Q3W	Unknown
EBC	524	174,992	202,869	125,761	1,015,088	116,615	295,355	47,047
MBC	155	36,044	63,886	22,516	888,912	76,469	214,116	15,294
EBC or MBC[a]	—	—	—	—	192,019	—	—	—
Total BC	**679**	**242,977**	**266,756**	**148,277**	**2,096,019**	**193,084**	**509,471**	**62,340**
MGC	44	22,041	16,898	0	121,897	6,652	28,301	11,112
Total	**723**	**265,018**	**283,654**	**148,277**	**2,217,916**	**199,736**	**537,772**	**73,452**

BC=breast cancer; EBC=early breast cancer; MBC=metastatic breast cancer; MGC=metastatic gastric cancer; Q1W=once a week; Q3W=every 3 weeks.

Note: Rounding errors may be introduced in the total figure.

[a] Exposure via the Patient Access Program is included.

Table 39 Cumulative Patient Exposure from Marketing Experience by Patient Sex and Age

	Sex			Age (years)			
Indication	**Male**	**Female**	**Unknown**	**2 to ≤16**	**>16 to 65**	**>65**	**Unknown**
EBC	3,672	455,346	1,060,218	-	354,782	104,236	1,060,217
MBC	2,447	286,761	686,853	—	193,680	95,394	686,853
EBC or MBC[a]	—	—	192,019	—	—	—	192,019
Total BC	**6,119**	**758,776**	**1,989,814**	—	**559,720**	**205,175**	**1,989,813**
MGC	31,323	14,741	114,815	—	27,178	18,886	114,815
Total	**37,442**	**773,517**	**2,104,629**	**—**	**586,898**	**224,061**	**2,104,628**

BC=breast cancer; EBC=early breast cancer; MBC=metastatic breast cancer; MGC=metastatic gastric cancer.

Note: Rounding errors may be introduced in the total figure.

[a] Exposure via the Patient Access Program is included.

PART II: MODULE SVI - ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have potential for misuse for illegal purposes are expected to share some general characteristics, such as psychoactive effects or, less commonly, anabolic effects or enhancement of hemoglobin levels. The lack of evidence of such side-effects make it highly unlikely that trastuzumab is misused for illegal purposes. To date, no reports of misuse of Herceptin for illegal purposes have been received.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not Applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not Applicable.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not Applicable.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of important identified risks and important potential risks

Information on important identified risks

1.1 CARDIAC DYSFUNCTION

Medical Dictionary for Regulatory Activities (MedDRA) Terms:

Cardiac Failure Standardised MedDRA Query (SMQ)—Wide

Potential mechanisms:

- There may be a feedback loop involving neuregulin and ErbB2 (as a co-receptor) as part of a cell (myocyte) survival pathway.
- Trastuzumab may block or alter cell survival signalling.
- Trastuzumab may down-regulate ErbB2 and thereby prevent cell survival signalling.
- Cardiac physiological stress or damage can be exacerbated by trastuzumab

Evidence source(s) and strength of evidence:

- MBC: Studies M77001 and BO16216.
- EBC: Joint Analysis (NSABP B-31 and NCCTG N9831), Studies BCIRG 006 (H2296s)/GO00773, BO16348, MO16432, BO22227, MO22982, MO28048, and BO20652
- GC: BO18255. QTc-study H4613g (HerQLes).
- Global Safety Database

Characterization of the risk:

Patients treated with Herceptin are at increased risk of developing CHF (New York Heart Association [NYHA] class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving Herceptin therapy alone or in combination with taxane following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S_3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Herceptin.

Background incidence/ prevalence:

- Metastatic Breast Cancer, First-line HER2-positive

The incidence of symptomatic CHF (Grades 3 or 4) for:

Non-trastuzumab containing regimens:

- Without anthracyclines: 0.3% to 1% (Slamon et al. 2001, Johnston et al. 2009)
- With anthracyclines: 3% to 4.7% (Slamon et al. 2001, O'Brien et al. 2004)

Trastuzumab containing regimens:

- Without anthracyclines: 2% to 4% (Slamon et al. 2001, Seidman et al. 2002).
- With concurrent anthracyclines: 16% (Slamon et al. 2001).

- Metastatic Breast Cancer, Second-line HER2-positive

Based on three lapatinib studies, the incidence of symptomatic CHF (Grades 3 or 4) was <1% for non-trastuzumab containing regimens (Blackwell et al. 2012; Capri et al. 2010; Burstein et al. 2003). In a pooled analysis of 3,689 lapatinib patients enrolled in clinical trials, the incidence of symptomatic cardiac toxicity by prior treatment was:

Anthracyclines: 0.5%

Herceptin: 0.1%

Neither anthracyclines or trastuzumab: 0.1%

- Early Breast Cancer, HER2-positive

Based on a review of three adjuvant Herceptin trials (NASBP B-31, NCCTG N9831, HERA) with anthracycline and non-anthracycline containing regimens, the incidence of symptomatic CHF (defined as NYHA Class III or IV) was:

0.8% to 3.8% for Herceptin containing regimens (Herceptin was given sequentially or concurrently).

0% to 0.9% for non-Herceptin containing regimens

Prevalence: Not available [(Tan-Chiu et al. 2005; Perez et al. 2008 ; Piccart-Gebhart et al. 2005)

- Advanced Gastric Cancer

Incidence

A recent randomised trial reported a 1.1% incidence of decreased LVEF (unspecified criteria) among HER2+ patients with advanced GC not treated with Herceptin (Van Cutsem et al. 2009).

Prevalence:

Not available

Frequency with 95% CI:

Frequency data for studies M77001, BO16216 and BO18255 is presented in Section 1.1 of Annex 7 Table 1, Table 2, Table 3 and Table 4 respectively. For BCIRG 006 (H2296s)/GO00773: Please refer to Table 7 to Table 10 in Annex 7.

BO16348 (HERA):

The primary endpoint was to investigate the potential predictive value of changes in blood levels of NT-pro BNP (and/or other neuro-hormones or cardiac markers) for progression to symptomatic CHF in patients who experience a significant LVEF drop (as defined in the HERA protocol), in the HERA trial: in total, 18/1682 (1.07%) patients in the Herceptin 1-year arm and 17/1673 (1.02%) patients in the Herceptin 2-year arm had a primary cardiac endpoint.

Secondary cardiac endpoint was:

- To determine, if changes in blood levels of NT-pro BNP (and/or other neuro-hormones or cardiac markers) correlate with outcome in patients experiencing congestive heart failure in the HERA trial.
- To investigate the potential predictive value of changes in blood levels of NT-pro BNP (and/or other neuro-hormones or cardiac markers) for development of symptomatic CHF in all patients in the HERA trial (regardless of LVEF drop).
- To determine if changes in blood levels of NT-pro BNP (and/or other neuro-hormones or cardiac markers) correlate with LVEF changes in the HERA trial.
- To investigate the potential diagnostic value of NT-pro BNP (and/or other neuro-hormones or cardiac markers) in patients experiencing dyspnoea (of uncertain cause) in the HERA trial.

There was a higher incidence of secondary cardiac endpoints in the Herceptin 2-year arm (137/1673 [8.19%] patients) compared with the Herceptin 1-year arm (85/1682 [5.05%] patients). A total of 15/1744 (0.86%) patients in the Observation only arm had secondary cardiac endpoints.

MO28048 (SafeHER)

In the primary safety analysis, cardiac AEs were reported by 428/2573 (16.6%) patients overall. The most frequently reported cardiac AE was decreased ejection fraction (119/2573 [4.6%] patients overall).

Decreased ejection fraction led to treatment discontinuation 48/2573 (1.9%) patients overall. Cardiac failure congestive was reported infrequently (0.4% of patients overall) and usually resulted in discontinuation of study treatment. In all cases except one ongoing event at clinical cut-off, patients made a full recovery from CHF.

Overall, 34/2573 (1.3%) patients reported a serious cardiac AE during the treatment period. Eleven serious cardiac AEs were coded as ‘cardiac failure, congestive’.

Overall, 128/2573 (5.0%) patients had an AE that led to permanent study drug discontinuation. The AE most frequently leading to discontinuation was ejection fraction

decreased (48/2573 [1.9%] patients overall), which accounted for all AEs reported in the Investigations System Organ Class (SOC).

Joint Analysis of B-31 and N9831:

Most cardiac events occurred within 15 months from starting paclitaxel ± Herceptin. At 3 years, the cardiac event rate was estimated at 3.16% in the doxorubicin plus cyclophosphamide followed by docetaxel plus Herceptin (AC→T + H) group, 0.90% in the doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) group, and 1.72% in the doxorubicin plus cyclophosphamide followed by docetaxel followed by Herceptin (AC→T→H) group. Between 5 and 7 years of follow-up, an additional patient in each treatment group experienced a cardiac event; the cardiac event rate at 9 years follow-up was estimated at 3.22% in the AC→T + H group, 1.04% in the AC→T group, and 2.02% in the AC→T→H group.

In the joint safety population, 35.8% of patients in the AC→T + H group and 32.7% of patients in the AC→T→H group experienced an absolute drop in LVEF of 10% points to below 55% compared with 25.4% of patients in the AC→T group.

Also in the joint safety population, 25.3% of patients in the AC→T + H group and 22.0% of patients in the AC→T→H group experienced an absolute drop in LVEF of 5% points to below the institution's lower limit of normal (LLN) compared with 17.4% of patients in the AC→T group.

The rates of symptomatic CHF were 3.1% in the AC→T + H group, 1.6% in the AC→T→H group, and 1.0% in the AC→T group, which is comparable to the CHF rates observed in the other large adjuvant studies where Herceptin followed anthracycline chemotherapy. With further follow-up, the per-patient incidence of new-onset cardiac dysfunction, as measured by LVEF, remains essentially unchanged. This updated analysis also shows evidence of reversibility of left ventricular dysfunction, with 64.5% of patients who experienced symptomatic CHF in the AC→T + H group being asymptomatic at latest follow-up, and 90.3% having full or partial LVEF recovery.

Neoadjuvant-adjuvant treatment in EBC

MO16432 (NOAH):

As expected, more patients in the HER2 positive + Herceptin + chemotherapy (TC) arm had a decline in LVEF during the chemotherapy period compared with patients in the other two arms who did not receive trastuzumab. Overall, only 13.3% of patients in the HER2 positive + TC arm showed no change or an increase in LVEF during chemotherapy compared with 27.5% of patients in the HER2 positive + C arm and 20.8% in the HER2 negative + C arm. However, most of the declines in LVEF were <10% points compared with baseline.

BO22227 (HannaH):

Please refer to Table 5 and Table 6 (Section 1.1 of Annex 7) or Table 40 and Table 41 below, which show the incidence of cardiac dysfunction-related AEs by severity for the Herceptin IV and Herceptin SC arms, respectively. In the new 5-year follow-up data, the overall incidence of cardiac dysfunction-related AEs was 19% in the IV arm and 16% in the SC arm.

The overall percentage of patients with at least one cardiac AE was similar in both study arms: 14.1% (42/298) of patients in the Herceptin IV arm and 14.8% (44/297) of patients in the Herceptin SC arm experienced 62 and 57 cardiac AEs (SOC Cardiac disorders and selected cardiac High Level Terms (HLTs) in the SOC Investigations), respectively Table 42.

Most AEs were from the SOC Cardiac disorders (a total of 41 patients in the Herceptin IV arm and 43 patients in the Herceptin SC arm experienced events in this SOC), with the remainder being abnormal cardiac function assessments reported as AEs under the SOC Investigation (experienced in 5 patients in the Herceptin IV arm and 2 patients in the Herceptin SC arm). In addition, as described in the Update Clinical Study Report (CSR) (Report No. 1057070, September 2013), an event of pleural effusion was reported in the Herceptin SC arm that coded primarily to the Respiratory, thoracic and mediastinal disorders SOC in which the contribution of underlying cardiac dysfunction could not be ruled out. This event is not included in the analyses of cardiac events.

The majority of cardiac AEs were Grade 1 or Grade 2 in intensity (59/62 events and 50/57 events in the Herceptin IV and Herceptin SC arms, respectively). A total of eight Grade 3 AEs were reported, two events in the Herceptin IV arm and six events in the Herceptin SC arm. No Grade 4 cardiac AEs were reported. For each of the treatment arms, one Grade 5 event of MI was reported. There was no marked imbalance in incidence between the treatment arms in any individual type of cardiac event. The most frequently reported AEs were rhythm disorders and left ventricular dysfunction Table 42.

Clinically significant cardiac AEs (i.e., those that were serious, severe, led to withdrawal or death, or were symptomatic of left ventricular systolic dysfunction) that occurred during treatment were discussed in detail in the Update CSR (Report No. 1057070, September 2013). One cardiac AE was reported during the survival follow-up phase.

Table 40 Cardiac Dysfunction, Severity & Frequency: BO22227 IV ARM

stae17cf_se Summary of CTC Grading (Worst Case) for Cardiac Failure - SMQ Broad (SMQ) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB IV; N = 298

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	56 (19)	43 (14)	16 (5)	-	-	-
Total Number of AEs	63	47	16	-	-	-
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Total Pts With at Least one AE	43 (14)	37 (12)	7 (2)	-	-	-
OEDEMA PERIPHERAL	30 (10)	27 (9)	3 (1)	-	-	-
OEDEMA	15 (5)	12 (4)	3 (1)	-	-	-
PERIPHERAL SWELLING	3 (1)	2 (<1)	1 (<1)	-	-	-
Total Number of AEs	48	41	7	-	-	-
CARDIAC DISORDERS						
Total Pts With at Least one AE	13 (4)	5 (2)	8 (3)	-	-	-
LEFT VENTRICULAR DYSFUNCTION	12 (4)	4 (1)	8 (3)	-	-	-
CARDIAC FAILURE	1 (<1)	1 (<1)	-	-	-	-
Total Number of AEs	13	5	8	-	-	-
INVESTIGATIONS						
Total Pts With at Least one AE	1 (<1)	-	1 (<1)	-	-	-
EJECTION FRACTION DECREASED	1 (<1)	-	1 (<1)	-	-	-
Total Number of AEs	1	-	1	-	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Total Pts With at Least one AE	1 (<1)	1 (<1)	-	-	-	-
NOCTURNAL DYSPNOEA	1 (<1)	1 (<1)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
AE17 03MAY2017:22:22:16 (1 of 2)

Table 41 Cardiac Dysfunction, Severity & Frequency: BO22227 SC ARM

stae17cf_se Summary of CTC Grading (Worst Case) for Cardiac Failure - SMQ Broad (SMQ) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB SC; N = 297

Body System/ Adverse Event	Total		CTC Grading 1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	47	(16)	38	(13)	7	(2)	3	(1)	-		-	
Total Number of AEs	52		41		7		4		-		-	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS												
Total Pts With at Least one AE	33	(11)	31	(10)	2	(<1)	-		-		-	
OEDEMA PERIPHERAL	23	(8)	22	(7)	1	(<1)	-		-		-	
OEDEMA	10	(3)	9	(3)	1	(<1)	-		-		-	
PERIPHERAL SWELLING	3	(1)	3	(1)	-		-		-		-	
Total Number of AEs	36		34		2		-		-		-	
CARDIAC DISORDERS												
Total Pts With at Least one AE	15	(5)	7	(2)	5	(2)	3	(1)	-		-	
LEFT VENTRICULAR DYSFUNCTION	10	(3)	4	(1)	5	(2)	1	(<1)	-		-	
CARDIAC FAILURE CONGESTIVE	2	(<1)	-		-		2	(<1)	-		-	
CARDIAC FAILURE	1	(<1)	-		-		1	(<1)	-		-	
DIASTOLIC DYSFUNCTION	1	(<1)	1	(<1)	-		-		-		-	
LEFT VENTRICULAR DILATATION	1	(<1)	1	(<1)	-		-		-		-	
RIGHT VENTRICULAR FAILURE	1	(<1)	1	(<1)	-		-		-		-	
Total Number of AEs	16		7		5		4		-		-	

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
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Table 42 Summary of Cardiac Events (SP)

stae11card_se Summary of Cardiac Adverse Events Including Selected HLTs (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	TRASTUZUMAB IV N = 298 No. (%)	TRASTUZUMAB SC N = 297 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	42 (14.1)	44 (14.8)
Total Number of AEs	62	57
CARDIAC DISORDERS		
Total Pts With at Least one AE	41 (13.8)	43 (14.5)
LEFT VENTRICULAR DYSFUNCTION	12 (4.0)	10 (3.4)
TACHYCARDIA	9 (3.0)	6 (2.0)
PALPITATIONS	4 (1.3)	6 (2.0)
SINUS TACHYCARDIA	3 (1.0)	3 (1.0)
BUNDLE BRANCH BLOCK RIGHT	1 (0.3)	2 (0.7)
DEFECT CONDUCTION INTRAVENTRICULAR	2 (0.7)	1 (0.3)
HEART VALVE INCOMPETENCE	2 (0.7)	1 (0.3)
ANGINA PECTORIS	1 (0.3)	1 (0.3)
AORTIC VALVE INCOMPETENCE	1 (0.3)	1 (0.3)
ARRHYTHMIA	-	2 (0.7)
ATRIAL FIBRILLATION	-	2 (0.7)
CARDIAC ANEURYSM	-	2 (0.7)
CARDIAC FAILURE	1 (0.3)	1 (0.3)
CARDIAC FAILURE CONGESTIVE	-	2 (0.7)
CARDIOMYOPATHY	1 (0.3)	1 (0.3)
CARDIOVASCULAR DISORDER	2 (0.7)	-
CORONARY ARTERY DISEASE	2 (0.7)	-
EXTRASYSTOLES	-	2 (0.7)
MYOCARDIAL INFARCTION	1 (0.3)	1 (0.3)
MYOCARDIAL ISCHAEMIA	1 (0.3)	1 (0.3)
PERICARDIAL EFFUSION	-	2 (0.7)
VENTRICULAR HYPOKINESIA	2 (0.7)	-
ARTERIOSCLEROSIS CORONARY ARTERY	-	1 (0.3)
ATRIAL FLUTTER	1 (0.3)	-
ATRIOVENTRICULAR BLOCK	1 (0.3)	-
ATRIOVENTRICULAR BLOCK FIRST DEGREE	-	1 (0.3)

(body system continuing ...)

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Selected from MedDRA SOC 'Cardiac disorders', HLTs
('CARDIAC FUNCTION DIAGNOSTIC PROCEDURES','CARDIAC IMAGING PROCEDURES','ECG INVESTIGATIONS','HEART RATE AND PULSE INVESTIGATIONS')
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Table 42 Summary of Cardiac Events (SP) (cont.)

stae11card_se Summary of Cardiac Adverse Events Including Selected HLTs (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	TRASTUZUMAB IV N = 298 No. (%)	TRASTUZUMAB SC N = 297 No. (%)
(... body system continuing)		
BRADYCARDIA	1 (0.3)	-
CARDIAC FLUTTER	-	1 (0.3)
CARDIOTOXICITY	-	1 (0.3)
DIASTOLIC DYSFUNCTION	-	1 (0.3)
DILATATION ATRIAL	1 (0.3)	-
LEFT ATRIAL ENLARGEMENT	1 (0.3)	-
LEFT VENTRICULAR DILATATION	-	1 (0.3)
LEFT VENTRICULAR HYPERTROPHY	-	1 (0.3)
MITRAL VALVE INCOMPETENCE	1 (0.3)	-
MITRAL VALVE PROLAPSE	1 (0.3)	-
MYOCARDIAL FIBROSIS	1 (0.3)	-
RIGHT VENTRICULAR FAILURE	-	1 (0.3)
SUPRAVENTRICULAR EXTRASYSTOLES	1 (0.3)	-
TRICUSPID VALVE INCOMPETENCE	1 (0.3)	-
VENTRICULAR ARRHYTHMIA	1 (0.3)	-
VENTRICULAR EXTRASYSTOLES	1 (0.3)	-
Total Number of AEs	57	55
INVESTIGATIONS		
Total Pts With at Least one AE	5 (1.7)	2 (0.7)
ELECTROCARDIOGRAM	2 (0.7)	-
REPOLARISATION ABNORMALITY		
EJECTION FRACTION	-	1 (0.3)
EJECTION FRACTION DECREASED	1 (0.3)	-
ELECTROCARDIOGRAM ABNORMAL	-	1 (0.3)
ELECTROCARDIOGRAM QRS COMPLEX ABNORMAL	1 (0.3)	-
HEART RATE INCREASED	1 (0.3)	-
Total Number of AEs	5	2

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Selected from MedDRA SOC 'Cardiac disorders', HLTs
('CARDIAC FUNCTION DIAGNOSTIC PROCEDURES','CARDIAC IMAGING PROCEDURES','ECG INVESTIGATIONS','HEART RATE AND PULSE INVESTIGATIONS')
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Observational study in EBC

BO20652 (OHERA)

Symptomatic CHF:

At the time of the final analysis, within the safety population, 106 of 3733 patients had developed symptomatic CHF (NYHA Class II- IV) prior to any recurrence of disease. This translates into a cumulative incidence of 2.8% (95% CI: 2.3-3.4%) and an incidence rate of 690 per 100,000 person-years (95% CI 568 -831).

Cardiac Death:

In the safety population, 6 of 3733 (0.2%) patients experienced a cardiac-related death without prior disease recurrence. The incidence of cardiac death, based on these 6 patients, was 0.2% (95% CI: 0.1% – 0.4%) and the incidence rate was 37 cardiac deaths per 100,000 person – years (95% CI: 14 – 80). Five patients (0.1%) experienced cardiac death after disease recurrence.

Seriousness/Outcomes

Clinical studies

- Metastatic Breast Cancer

In Study M77001 (CSR 1011941), There were a total of 12 possible cardiac related adverse events (mainly tachycardia and palpitations) reported in the Herceptin + docetaxel arm as compared with 3 in the docetaxel alone arm. Most of these events were non-serious (common toxicity criteria [CTC] grade 1 and 2). The majority of the AEs resolved. However, there were two fatal cases (2%) of CHF in the Herceptin + docetaxel arm.

In another study, BO16216, where trastuzumab along with anastrozole reported a total of four AEs (2 resolved) in anastrozole alone arm, 16 AEs (11 resolved) in anastrozole plus trastuzumab arm, and 10 AEs (3 resolved) in anastrozole alone after start of trastuzumab arm. No cardiac deaths were reported.

- Early Breast Cancer Adjuvant Treatment

In Study BCIRG-006, the most frequently occurring symptomatic cardiac event was Grade 3/4 cardiac left ventricular function (CLVF).

The incidence was highest in the AC→TH arm (1.9%) compared with AC→T (0.3%) and docetaxel plus carboplatin plus trastuzumab (TCH) arms (0.4%) arms.

In a 10-year median follow-up study, BO16348 (HERA), the most prominent cardiac SAE was cardiac failure congestive in Herceptin-1-year (reported in 19/1682 patients [1.1%]) and Herceptin-2- year arms (reported in 24/1673 patients [1.4%]). The 10-year median follow-up data reports death due to cardiac failure congestive occurred in seven patients at different follow-up intervals. In the trastuzumab containing arms, cardiac failure congestive and peripheral swelling were the serious cardiac AEs leading to dose interruption and cardiac failure congestive was the most common cardiac serious AE leading to drug discontinuation.

Similarly, Study MO28048 (SafeHER) reported that the most frequently reported cardiac SAE was cardiac failure congestive in 12 patients. In 10/12 patients, the SAE of cardiac failure congestive led to drug discontinuation. No fatal events were reported.

In Joint Analysis of NSABP B-31 and N9831, as of 10 March 2015, cardiac deaths were experienced by 2 patients (0.1%) in the AC→T + H group, 1 patient (0.3%) in the AC→T →H group, and 5 patients (0.3%) in the AC→T group. Sixty-four patients in AC→T + H group, 7 patients in the AC→T→H group, and 21 patients in the AC→T group reported cardiac left ventricular events. These AEs were not assessed as leading to study treatment withdrawal and/or discontinuation on the AE case report form (CRF) for either B-31 or N9831. The AEs leading to dose adjustment and outcomes of AEs were also not collected.

- Neoadjuvant-adjuvant Treatment in EBC

In Study MO16432 (NOAH), trastuzumab was administered concurrently with an anthracycline in neoadjuvant-adjuvant settings; the incidence of symptomatic cardiac dysfunction was low in the HER2+TC arm. Only 4 patients in the HER2+TC group had a decline in LVEF of ≥10% points to an LVEF of <50% and in only one of these patients (none in the other two groups) did the LVEF decline to <45%.

Study BO22227 compared Herceptin SC versus Herceptin IV in women with HER-2 positive early breast cancer. In the Herceptin IV arm, none of the events of cardiac dysfunction is reported serious and 56 of the 63 AEs resolved without sequelae. In Herceptin SC arm, two AEs (2 events of cardiac failure congestive) were assessed as serious. The most frequently reported Preferred Terms (PTs) were the same with the SC as for the IV formulation but with fewer AEs in the SC arm. There were no reports of fatal outcome from a cardiac dysfunction-related AE for both formulations.

In PrefHER Study (MO22982), the most frequently reported AEs in Herceptin IV (4 cycles) arm were left ventricular dysfunction (in 5/478 patients [1.05%]) and bradycardia (in 3/478 patients [0.63%]), palpitations, and ejection fraction abnormal (in 2/478 patients each [0.42%]). In Herceptin SC arm, the most frequently reported AEs were palpitations (in 3/479 patients [0.63%]), ejection fraction decreased (in 3/479 patients [0.63%]), and left ventricular dysfunction and cardiac failure congestive (each reported in 2/479 patients each [0.42%]). In Herceptin IV continuation period (Cohort 1, 226 patients)

Cardiac AEs were reported for 7/226 patients (3.1%) and none of them were left ventricular systolic dysfunction or CHF events. None of the cardiac AEs were serious or Grade ≥3 events, or led to withdrawal from treatment. No Cardiac AEs were reported for SID self-administration for SC SID period. In Cohort 2, SC vial continuation, Cardiac AEs were reported for 8/208 patients (3.8%). Four patients experienced left ventricular dysfunction and 3 patients cardiac failure congestive. In Cohort 2, IV continuation, Cardiac AEs were reported for 1/10 (10.0%) patients (Grade 1 event) and no left ventricular systolic dysfunction events were reported during the IV continuation period.

Please refer to Section 1.2 of Annex 7 for detailed study wise data on seriousness and outcomes.

Global Safety Database

The information that was retrieved from the MAH's Global Safety Database, utilizing the MedDRA SMQ Cardiac failure (wide), is cumulative through24 September 2018. A total of 10,262 AEs (reported in 9,337cases) were retrieved, of these 6,810 (66. 4%) AEs were reported as serious by the reporter and/or the MAH. Based on the exposure of Herceptin (until 24 September 2018, the data-lock point of the 2018 PBRER report number 1089226) in 2,935,329 patients, the crude reporting rate of cardiac AEs is 0.3%. The Summary Table of Adverse Events by SOC is presented in Table 12 (Annex 7). The most frequent SAEs were distributed as follows: ejection fraction decreased n=2,911 (42.7% of all SAEs in this identified risk group); cardiac failure n=1,460 (21. 4%); cardiac failure congestive n=770 (11.3%); left ventricular dysfunction n=489 (7. 2%); and cardiac dysfunction n= 264 (3.9%).

A total of 175 AEs (1.7% of all AEs in this identified risk group) resulted in a fatal outcome. Of the AEs with a fatal outcome, the most frequently reported were as follows: cardiac failure (n=66; 37.7 % of all fatal outcome AEs); cardiac failure congestive (n=38; 21.7%); ejection fraction decreased and cardiopulmonary failure (n=12; 6.3% each); ejection fraction decreased n=11, 6.3%)

A favorable outcome was reported in 3,543 (34.5%) of the 10,262 total AEs, having resolved/resolving/resolved with sequelae. For 4,831(47.1%) AEs, the outcome was either not reported or reported as unknown. The outcome was reported as not recovered/not resolved in 1,615(15.7%) AEs Refer to Table 13 (Annex 7).

Trastuzumab treatment was maintained in response to the AE in 1,074 (10.8%) of the total reported drug events in the cardiac dysfunction risk group. It was withdrawn in 3,467(33.5%) of the reported drug events and the action taken in response to the event was unknown in 3,692(38.3%) drug events. The dose was interrupted for 942 (9.1%) drug events and the dose was reduced for 28 (0.27%) AEs. The dose was increased in 1 (0.01%) drug events and modified in 34 (0.034%) drug events (Table 14; Annex 7).

Severity and nature of risk

- Metastatic Breast Cancer

In Study M77001, eight Grade 3 AEs (8.5%) in the docetaxel alone arm and four (4.3%) in the trastuzumab + docetaxel arm were reported. No Grade 4 or 5 AEs were reported in either arm. In Herceptin containing arm, more Grade 1 AEs were reported in patients with age ≤50 years compared with patients with age >50 years (34.3% versus 21.1%); Grade 2 AEs were reported more frequently in the sub-group of patients >50 years (11.4% versus 22.8%). In the Herceptin containing arm, Grade 3 AEs were only reported in patients with age ≤50 years (5.7%). No Grade 4 or 5 AEs were reported in any arm. No discernible pattern seen in either of the age groups.

In Study BO16216, four Grade 3 AEs (3.8%) were reported in the anastrozole alone arm and two Grade 3 AEs (1.9%) were reported in the anastrozole plus Herceptin arm. In patients ≤50 years of age, cardiac AEs were 3.1% for anastrazole arm, 11.1% for anastrazole + Herceptin arm, and 16.7% for anastrazole alone after start of Herceptin arm compared to 1.4%, 11.8%, and 12.5% respectively in patients >50 years of age. Most cardiac events reported in age ≤50 years were of Grade 2, while those in age group >50 years were predominantly Grade 1 events. No Grade 4 or 5 events were reported in any of the age groups. A meaningful interpretation of the data is impacted by low event counts across both groups.

- Early Breast Cancer (Adjuvant Treatment)

BCIRG 006 (H2296s)/ GO00773:

The data were stratified for age and region. Across all the treatment arms, patients in age group >50 years reported higher percentage of "Any symptomatic or clinical significant asymptomatic cardiac events" (all assessment) compared with age group ≤50 years. In patients >50 years of age, cardiac AEs were 5.9% for AC—>T arm, 13.2% for AC—>TH arm, and 5.4% for and TCH arm, compared to 3.5%, 9.6%, and 4.6% respectively in patients ≤50 years of age. In AC—>T arm, the highest percentage of cardiac events were reported in North American patients, followed by Middle Eastern and European (section 1.3 of Annex 7). In the AC—>TH arm, the highest percentage of cardiac events were observed in South African patients, followed by South American and North American patients. In the TCH arm, the highest percentages of cardiac events were observed in North American patients, followed by South Africa and South America. The number of Grade 3-4 events reported was low and precluded meaningful comparison between the sub groups. There was no discernible pattern observed in the Herceptin containing treatment arms across region.

BO16348 (HERA):

In a 10-year median follow-up Study, BO16348 (HERA), across the three study arms, AEs within the cardiac dysfunction risk were mainly mild-to-moderate in severity,

comprising Grades 1 and 2 of severity. In all of the clinical trial arms, the most commonly occurring Grade 1 and Grade 2 AEs were Oedema Peripheral, Cardiac Failure congestive and Ejection Fraction decreased. No Grade 3 AEs were reported in the Observation arm. Cardiac Failure congestive was the most common Grade 3 AE in all of the trastuzumab-containing arms: trastuzumab 1-year: 13/1682 (0.8%) patients; trastuzumab 2-year: 10/1673 (0.6%) patients. The other Grade 3 AEs in the trastuzumab-containing arms occurred at a frequency of < 0.1%. The most commonly occurring Grade 4 AE was Cardiac Failure congestive and it was observed in the trastuzumab 1-year and 2-year arms (4/1682 (0.2%) and 8/1673 (0.5%) patients , respectively), as well as the Observation only arm (1/1744 (0.1%) patients).

The AEs of cardiac dysfunction were stratified by the age and race (section 1.3 of Annex 7). The >50 years subgroup reported higher percentage of patients with AEs compared with the <50 years subgroup in all the three arms. For all age groups, majority of the AEs were either Grade 1 or 2 in line with the unstratified outputs. Similarly, across all the race sub-groups, majority of the events reported were Grade 1 and Grade 2. A meaningful interpretation of the data is impacted by low event counts across other race sub-groups.

MO28048 (SafeHER):

Overall, the cardiac dysfunction risks were mainly mild-to-moderate in severity, comprising of Grades 1 and 2 events. The most commonly occurring Grade 1 AEs were oedema peripheral, peripheral swelling and ejection fraction decreased. The most commonly occurring Grade 2 AEs were ejection fraction decreased and oedema peripheral. Cardiac failure congestive and ejection fraction decreased were the most commonly occurring Grade 3 events. Cardiac failure congestive and pulmonary oedema were the Grade 4 events. No Grade 5 fatal events were reported.

The AEs of cardiac dysfunction were stratified by the age and race (section 1.3 of Annex 7). The >65 years sub-group reported higher percentage of patients with AEs compared with the ≤65 years sub-group. For all age groups, majority of the AEs were either Grade 1 or 2 in line with the unstratified outputs. Majority of the patients included in the trials were White. Across all the race sub-groups, majority of the events reported were Grade 1 and Grade 2.

Joint Analysis of NSABP B-31 and N9831:

Of the Cardiac dysfunction AEs (as defined in this RMP), only severity data on Cardiac – left ventricular function and Oedema were collected for both Studies B-31 and N9831, i.e., no severity data was collected for CHF, decreased (LV)EF, or other Cardiac failure SMQ AEs. The distribution of AEs across all the arms are presented in section 1.3 of Annex 7. A total of three cardiac deaths were observed in the trastuzumab-containing arms compared with five cardiac deaths in the control arm. These cardiac deaths did

not necessarily include CHF (i.e., the category of cardiac death in the Joint Analysis included MI, arrhythmia, and sudden death).

The AEs of cardiac dysfunction were stratified by the presence of number of known risk factors (age >50 years, use of anti−hypertensive medications at baseline, and LVEF at paclitaxel baseline ≤55%), and by race (section 1.3 of Annex 7). In this study, majority of patients were White. Other substantial groups included were Black and Hispanic. Most of these patients were in the AC –>T or AC –>T+H arm. The stratification by race, in patients with 0, 1, 2, or all the 3 of these risk factors is presented in Section 1.3 of Annex 7. A meaningful stratified comparison of cardiac dysfunction by race is impacted by low number of patients and AEs in most of the resulting subgroups.

- Neoadjuvant-adjuvant treatment in EBC

MO16432 (NOAH):

Cardiac events reported in at least two patients included: angina pectoris (5 patients in each of the HER2-positive arms), tachycardia (5 patients in each of the HER2-positive arms and one patient in the HER2-negative arm) and palpitations (3 patients in each of the HER2-positive arms and one patient in the HER2-negative arm). None of these cardiac events were reported as Grade 3 or 4 AEs. The myocardial ischemia in the HER2+TC arm was of Grade 2 intensity at worst and recovered on the same day without sequelae.

During the post-operative period, 16 patients experienced 22 cardiac AEs (8.9% [10/112] patients with 15 AEs in HER2 positive + TC, 10.0% [2/20] patients with two AEs in HER2 positive + C→T, 5.9% [4/68] patients with five AEs in HER2 positive + C). In the HER2 positive + C arm, patient [redacted] experienced a Grade 3 pericardial effusion and in the HER2 positive + TC arm, patient [redacted] had a Grade 3 decreased ejection fraction considered related to study medication and reported as an SAE.

- Neoadjuvant-adjuvant Treatment in EBC

BO22227 – (HannaH):

Severity per CTC Grading

In the IV arm, all AEs were either Grade 1 or Grade 2; there were no Grade 3 -5 AEs. In the Herceptin SC arm, 4 AEs in 3 patients were Grade 3 in severity; two of these were assessed as serious. One patient in each of the treatment arms experienced a Grade 5 event of myocardial infarction. The 5-year follow-up data with last patient last visit (LPLV) of 24 January 2017 did not show any change in the data presented.

The AEs of cardiac dysfunction were stratified by the age and race. No clear discernible pattern was observed in either of the age groups (age ≤50 and >50 years sub-groups)

for cardiac dysfunction-related events. In Asian patients 30% and 27% of patients (IV, SC) had events, white 16% and 13%, other 17% and 15%.

MO22982 (PrefHER):

Results from crossover period SC-IV or IV-SC (479 patients for Herceptin SC period and 478 patients for Herceptin IV period).

Herceptin IV (4 cycles):

Two patients with grade 3 Left Ventricular Dysfunctions were reported. Three patients had three Cardiac AEs of Grade 2 severity and eleven had 12 Grade 1 AEs.

Herceptin SC (4 cycles):

One patient with grade 3 left ventricular dysfunction was reported. Two patients had two Cardiac AEs of a Grade 2 severity and nine patients had 12 Grade 1 AEs.

- Advanced Gastric Cancer

BO18255 (ToGA):

Across treatment arms, Fluoropyrimidine/Cisplatin arm and Trastuzumab/ Fluoropyrimidine/ Cisplatin arm, cardiac AEs were mostly mild-to-moderate in severity.

The AEs of cardiac dysfunction were stratified by the age, gender, race, and region (section 1.3 of Annex 7). The stratified data from this study confirms that the age >50 years has an identified risk factor for cardiac dysfunction. The percentage of AEs was more in female patients. No Grade 3 or 4 AEs were reported in female patients. The Oriental patients reported higher numbers of AEs compared with the Caucasians; majority of them were Grade 1. The meaningful comparison of Grade 2, 3, and 4 events is impacted by low numbers of events reported in each of these sub-groups. In the Herceptin containing arm, Asian patients reported the most number of Grade 1 AEs as compared with the European patients (25/164, 16.1% versus. 3/99, 3%). A relatively lower number of Grade 2 (Asia: 3, 1.9%; Europe: 3, 3%), Grade 3 (Asia: 1, 0.6%; Europe: 1, 1%), and Grade 4 (Asia: 2[1.3%], Europe: none) events were reported precluding a meaningful analysis.

Observational study in EBC

OHERA

The median age was 55 years (range: 21 – 86 years). Almost all the patients were female (3722 patients, 99.7%) and had Stage I or II breast cancer (3093 patients, 82.9%). Two-thirds of the patients were ER positive (62.6%).

Symptomatic CHF

Of the 106 patients with symptomatic CHF, (38 patients [1.0%]) were reported to have moderate to severe symptomatic CHF (NYHA Class III/IV), of which 1 patient died due to symptomatic CHF.

Please refer to Annex 7 for detailed study wise data on severity and nature of risk.

Impact on individual patient:

Cardiac failure may have a significant impact on the quality of life of individual patients. Treatment with trastuzumab should be suspended if LVEF percentage drops ≥ 10 points from baseline AND to below 50 %, and a repeat LVEF assessment should be performed within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of Herceptin should be strongly considered in order to avoid progression to CHF, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed-up. In the majority of patients, LVEF decrease is reversible.

Risk group or risk factors

Early Breast Cancer (EBC):

BCIRG 006 (H2296s)/ GO00773:

Patient characteristics and clinical assessments specific to cardiac safety were analyzed to determine whether risk factors for a cardiac event could be identified. Variables that were evaluated include treatment received (AC→T versus. AC→TH), age, nodal status, prior or current use of cardiovascular medications at baseline, radiation to left side of the chest, baseline LVEF, on-study LVEF as characterized by LVEF at docetaxel baseline, LVEF value at least 28 days prior to an event (continuous time-varying), and LVEF value <55 at least 28 days prior to an event (continuous dichotomous).

The risks of both symptomatic and asymptomatic LVEF events following initiation of treatment were increased with lower on-study LVEF values. Older patients (>50 years old) had an increased risk of both symptomatic cardiac and asymptomatic LVEF events regardless of treatment received.

No significant treatment-by-covariate interactions were detected.

The variables that remained significant in the multivariate model were treatment with AC →TH, age >50, and an LVEF value of <55% at least 28 days prior to the event. All covariates were associated with an increased risk of a cardiac event. Refer to Table 17 (Annex 7).

Risk Factor Modelling

BCIRG 006 (H2296s)/ GO00773

Asymptomatic LVEF events were defined as an absolute decrease of >15% in LVEF from baseline and to a value below an institution's law of large numbers (LLN). The analyses herein are of time to first symptomatic cardiac event per the individual case report form (ICRF) and/or asymptomatic LVEF events.

Patients who had an absolute LVEF decline of >15% from baseline during AC therapy had an approximately 6-fold increased risk of developing a cardiac event after initiation of T, TH, or TCH (p 0.0018; 95% CI: 1.9, 18.8). However, caution must be exercised in the interpretation of this association, as the decline in LVEF during AC treatment may be a factor used by the Independent Cardiac Review Panel (ICRP) to subsequently confirm a symptomatic cardiac event.

A 10-percentage point lower LVEF at the initiation of T, TH, or TCH at baseline resulted in a 1.5-fold increase risk of developing an event. Refer to Table 18 (Annex 7).

BO16348 (HERA):

Among the variables evaluated in univariate and multivariate Cox models to identify factors associated with an increased risk of a primary or secondary cardiac endpoint, Herceptin treatment, screening LVEF <60 EF points and, to a lesser extent, prior or current use of cardiovascular disease medication at baseline were significant risk factors[2].

Joint Analysis of B-31 and N9831:

Clinically meaningful cardiac event risk factors identified by subgroup included age and LVEF values at paclitaxel baseline as shown in Table 17 (Annex 7). The use of anti-hypertensive medications at baseline or during study was no longer a significant factor.

Table 19 (Annex 7) presents the incidence of cardiac events by the number of risk factors following initiation of paclitaxel or Herceptin + paclitaxel Therapy. The risk factors considered were age >50 years, the use of anti-hypertensive medication, and LVEF ≤55%.

Herceptin therapy, enrolment in Study B-31, and age >50 years were associated with an increased risk of a cardiac event in the AC→T + H group compared with the AC→T group. A lower LVEF, whether at baseline or ≥28 days prior to an event, was associated with an increased risk of CHF.

[2] BO16348 (HERA) CSR Report 1044055.

Patients in the AC→T + H group had an estimated 3.4-fold higher risk ($p< 0.001$, 95% CI 1.8, 6.1) of a cardiac event compared with patients in the AC→T group.

Patients >50 years of age had a 2.21-fold increased risk ($p=0.0011$, 95% CI 1.4-3.6) of a cardiac event compared with women ≤50 years of age. While the results suggest a large relative risk, the incidence of these events was relatively low.

A patient whose LVEF value (≥28 days prior to event) was 10-percentage points lower than another patient (everything else being equal) resulted in a 2.87-fold—$(1/0.90)^{10}$—increase in the risk of an event.

H4613g:

Trastuzumab did not prolong the QTc interval duration, and there was no apparent relationship between serum trastuzumab concentrations and the change in QTcF interval durations over time.

Trastuzumab had no clinically relevant effect on heart rate, uncorrected QT, PR, or QRS interval duration, and no cases of clinically significant abnormal U-wave or T-wave changes from baseline were observed.

Concomitant medication with carboplatin did not influence the pharmacokinetics of trastuzumab and vice versa.

MO28048 (SafeHER)

A greater proportion of patients in the highest weight quartile experienced cardiac AEs (21.3%) compared with other weight quartiles (proportions ranged from 12.3% to 18.9%). Of note, these upper weight quartile patients had a higher proportion of active medical conditions at baseline, with a marked imbalance for vascular disorders (44.6% in the highest weight quartile and between 17.6% and 29.8% for other weight quartiles) as well as for cardiac disorders (9.6% of patients in the highest weight quartile and between 5.3% and 9.4% for other weight quartiles).

BO20652 (OHERA)

Risk Factors for Symptomatic CHF:

Patients who experienced symptomatic CHF had more risk factors than non-CHF patients. More than half of the patients who experienced CHF (66.0%) had at least one medical condition representing a risk for symptomatic CHF compared to non-CHF patients (41.5%). At baseline, a higher proportion of patients who had symptomatic CHF were reported to have high blood pressure, diabetes mellitus, arrhythmias, cardiac valvular disorders, and other major cardiac/non-cardiac diseases or conditions (e.g., asthma, Chronic Obstructive Pulmonary Disease (COPD), aortic aneurysm, diastolic

dysfunction, embolism, etc.) compared to non-CHF patients. In addition, patients with symptomatic CHF were older compared to patients without CHF (median age 63 years versus. 55 years) and more were overweight/obese (body mass index [BMI]≥25 kg/m2) (61.3% versus. 51.7%). Patients with symptomatic CHF also had more often a diagnosis of asymptomatic CHF (NYHA Class I) at study entry compared to non-CHF patients (3.8% versus. 0.9%).

The incidence of symptomatic CHF was higher in patients with the following baseline characteristics; pre-existing cardiac condition, use of cardiovascular medications at study entry, hypertension or high blood pressure, baseline LVEF ≤ 55%, overweight/obese (i.e., BMI≥ 25 kg/m 2), age ≥ 65 years, and history of cardiac failure or active cardiac failure at study entry.

Risk Factors for Cardiac Death:

When restricting to patients without disease recurrence, of the 6 patients that died due to a cardiac-related event, these patients were in the age range of 46-74 years, and 5 out of 6 patients had a previous cardiovascular medical condition.

Preventability:

In the prescribing information, the MAH describes the need for cardiac function assessment, periodic LVEF monitoring, and management of cardiac dysfunction.

Impact on the benefit-risk balance of the product:

The review of the latest available data did not lead to any change in the benefit-risk profile of Herceptin.

Public health impact

The safety concern of cardiac dysfunction does not have a potential public health impact.

1.2 ADMINISTRATION-RELATED REACTIONS (ARRS)

MedDRA terms:

'Modified Anaphylactic Reaction basket' which consists of the Anaphylactic Reaction SMQ plus the individual PTs: Infusion-Related Reaction; and Injection Site Hypersensitivity, Hypersensitivity and drug hypersensitivity.

Potential mechanism:

The potential mechanism of administration-related reactions have not been clearly established. However, Calogiuri et al. 2009 hypothesize that such reactions (to monoclonal antibodies in general) are attributable to Beta-type reactions: immediate and delayed hypersensitivity; Gamma-type reactions: over-reactions or depression of the immune functions like the immunodeficit, autoimmune or allergic phenomena; but that other mechanisms such as a specific release of cytokines, might be also involved.

Evidence source(s) and strength of evidence:

- EBC: Studies BO16348, BO22227, MO22982, and MO28048.
- Global Safety Database.
- Drug Safety Reports (DSR): DSR 1036301 dated 12 December 2009, DSR 1056779 dated 27 June 2013 and DSR 1060413 dated 15 May 2014

Characterization of the risk:

Frequency with 95% CI

Adjuvant Treatment in EBC

- BO16348 (HERA)

The frequency for corresponding grades of AEs under ARR is presented in Table 43. The most frequently occurring AEs were cough (n=62; in observation only arm, n=117; in Herceptin 1 Year arm and n=147 in Herceptin 2 Year arm) and dyspnoea (n=46; in observation only arm, n=83; in Herceptin 1 Year arm and n=117; in Herceptin 2 Year arm).

Table 43 HERA (BO16348) Infusion-Related Reactions (IRR)/ARR Frequency and severity

Arm	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Observation only N =1744	217	149 (68.7)	63 (29.0)	3 (1.4)	1 (0.5)
Herceptin 1 Year N = 1682	569	405 (71.2)	146 (25.7)	15 (2.6)	2 (0.4)
Herceptin 2 Year N = 1673	736	521 (70.8)	191 (26.0)	17 (2.3)	1 (0.0)
MedDRA The Modified Anaphylactic Reaction SMQ consists of the Anaphylactic Reaction SMQ plus the individual PTs: Infusion-Related Reactions; and Injection-Site Hypersensitivity, Hypersensitivity and drug hypersensitivity. Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual. Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.					

- MO28048 (SafeHER)

1020 out of 2573 (39.6%) patients reported a total of 1494 events. These events were mainly skin and subcutaneous tissue disorders (594 [23.1%] patients) and respiratory, thoracic and mediastinal disorders (418 [16.2%] patients). The most frequently occurring administration related events were rash reported in 257/2573 (10.0%) patients, cough reported in 254/2573 (9.9%) patients and erythema in 234/2573 (9.1%) patients. Refer to Table 21 (Annex 7) for more details. In the overall safety population, 43 Grade ≥ 3 ARRs were reported in 35/2573 (1.4%) patients.

Neoadjuvant-adjuvant Treatment in EBC

- BO22227 (HannaH)

In the IV arm, the most frequently reported AEs were Rash (44); Pruritus (27); Cough (24), and Dyspnoea (22);

The overall incidence (all AEs, all grades) was 37.2% in the IV arm and 47.8% in the SC arm. The incidence of patients with grade 1 events was 31.5% in the IV arm compared to 40.7% in the SC arm, while the incidence of patients with grade 2 events was 11.4% in the IV arm compared to 16.8% in the SC arm thus difference in overall incidence was largely driven by more non-severe grade 1 and 2 events in the SC arm compared to the IV arm.

In the subcutaneous arm, five AEs were reported as NCI Common Terminology Criteria for Adverse Events (CTCAE) (version 3) grade 3, and six respectively in the IV arm. The most frequently reported AEs were the same with the SC formulation as for the IV formulation and were in similar order of frequency: Rash (48); Cough (35); Pruritus (26), and Dyspnoea (21).

Table 22 and Table 23 in Annex 7 show the incidence of ARR events according to severity.

No additional data on ARRs was available in the final CSR (based on the 5-year follow-up data, LPLV 24 January 2017) as ARRs are events which occur, during the treatment phase and as such, full information on these events was presented in the primary updated CSR (Report number 1057070).

Seriousness and outcomes

Early Breast Cancer (EBC)

Adjuvant Treatment:

- BO16348 (HERA)

Administration-related reaction was defined under the basket of modified anaphylactic reactions. Across all treatment arms, 25 patients reported SAEs of ARR. Observation Only (n=1744): 11/1744 (0.6%) patients; Herceptin 1-year (n=1682): 7/1682 (0.4%) patients and Herceptin-2-year (n=1673): 7/1673 (0.4%) patients, The reported SAEs in the 1-year Herceptin arm included 2 events of hypotension reported in 2 patients and one event each reporting urticaria, anaphylactic shock, cardiac arrest, cough, rash generalized and throat tightness. The 2-year treatment arm included 3 events of dyspnea reported in 3 patients, and one event each reporting erythema, urticaria, asthma, hypotension and anaphylactic reaction. No case of ARRs with fatal outcome was reported.

Hypotension, rash generalized, throat tightness, erythema and anaphylactic reaction were the ARRs leading to dose interruption in the trastuzumab-containing arms: Herceptin-1-year: 3 patients in1682 (0.2%) and Herceptin-2-year: 2 patients in 1673 (0.1%).

Hypotension and dyspnoea were the cardiac AEs leading to drug discontinuation in the trastuzumab-containing arms: Herceptin 2-year: 2/1673 (0.1%) patients.

- MO28048 (SafeHER)

As of 10 March 2015, a total of 17 SAEs in 16 patients were reported for administration-related reactions. The most frequently reported event terms for administration related SAEs were asthma in three patients, rash, drug hypersensitivity, hypersensitivity, anaphylactic shock and dyspnea are reported by 2 patients each.

Neoadjuvant-adjuvant Treatment in EBC

- BO22227 (HannaH)

The data presented below take into account the most severe intensity reported for multiple occurrences of the same adverse event in a given individual patient. For each AE Preferred Term and patient, the event is counted only once per patient and the worst outcome is counted.

Herceptin IV (n=298)

A total of 200 events were reported in 111 patients falling under the definition of Administration-related reaction. Six AEs were reported as NCI CTCAE (version 3) Grade

3, thereof 2 AEs were also reported as SAEs (PT: Hypersensitivity). Both events of Hypersensitivity were related to use of docetaxel leading to its discontinuation in 1 event. In 1 event, there was no docetaxel modification. Both events lasted ≤ 1 day and no action was taken with regards to Herceptin administration. 199 AEs were reported to have resolved. One AE was reported as unresolved.

Herceptin SC (n=297)

A total of 234 events were reported in 142 patients. None of the events was reported as serious. 230 AEs were reported to have resolved. One AE resolved with sequelae. Three AEs were reported as unresolved.

- MO22982 (PrefHER[3])

Results from crossover period SC-IV or IV-SC

Herceptin IV (4 cycles):

A total of 38 events in 31 out of 478 patients were reported falling under the definition of Administration-related reaction. The most frequently reported AEs were erythema, rash and cough (in 6 patients each), dyspnoea (in 5 patients) and pruritus (in 3 patients).

Herceptin SC (4 cycles):

A total of 90 events in 61 out of 479 patients were reported falling under the definition of Administration-related reaction.
The most frequently reported AEs were erythema (in 17 patients), cough and dyspnoea (in 9 patients each), rash (in 8 patients), flushing (in 7 patients), Dyspnoea (n=12 in 9 patients), Refer to Table 24 (Annex 7).

Results from Herceptin continuation period

Cohort 1: A total of 226 patients in Cohort 1 received 1239 Herceptin IV cycles during the IV continuation period and 43 patients received 98 cycles administered with the SC SID during the SID self-administration period. All ARRs reported during the continuation period of Cohort 1 were Grade 1 or 2 in severity

IV continuation: ARRs AEs were reported for 12/226 (5.3%) patients during IV continuation period.

SID self-administration: ARRs were reported for 1/43 (2.3%) patients (erythema). There were no AEs leading to discontinuation of trial drug during the SID self-administration period.

[3] Data has been presented as per PrefHER CSR

Cohort 2

Patients in Cohort 2 (SC Vial) continued to receive Herceptin SC via handheld syringe to complete their remaining cycles after the crossover period. A total of 208 patients in Cohort 2 received 1152 cycles with SC Vial during the SC continuation period and 10 patients received 34 cycles with IV during the IV continuation period. All ARRs reported during the continuation period of Cohort 2 were Grade 1 or 2 in severity.

IV continuation: No ARRs were reported for IV continuation in Cohort 2.

SC vial continuation: 28 ARRs were reported for 22 out of 208 patients. The most frequently reported AEs were erythema and cough (in 6 patients each) and rash (in 3 patients).

Global Safety Database

The information retrieved from the MAH's Global Safety Database, utilizing the Modified Anaphylactic Reaction MedDRA basket, is cumulative through 31 August 2017 (Table 26 in Annex 7).

A total of 16,654 AEs (reported in 12,840 cases) were retrieved (Table 26; Annex 7). Of these, 5,316 (32.1%) AEs were assessed as serious by the reporter and/or the MAH. The most frequent serious PTs were as follows: dyspnoea (n=1,348; 25.4%), infusion related reaction (n=471; 8.9%) and rash (n=335; 6.3%). Based on the exposure of Herceptin (upto 24 September 2018, the data-lock point of the 2018 PBRER report number 1089226) in 2,935,329 patients, the crude reporting rate of ARRs is 0.4%

A total of 391 AEs (2.4% of all AEs) had a fatal outcome. Of these, the most frequently reported PTs were as follows: respiratory failure (n=110, 28.1% of all fatal outcomes); cardiac arrest and dyspnoea (n=63; 16.1%each); and cardio-respiratory arrest (n=35; 9. 0%).

A favorable outcome was reported in 6,798 AEs (40. 8% of the 16,654 total AEs), having resolved/resolving/resolved with sequelae. There were 6,678 AEs (41.0%) that had an unknown or unreported outcome. The overall AE outcomes are shown in Table 27 of Annex 7.

Trastuzumab treatment was maintained (i.e., dose not changed) in response to the drug event in 3,441 (20.4%) of the reported drug events. It was withdrawn in 2,521(15.0%) of the reported drug events, and the action taken in response to the event was unknown in 8.398(50.0%) of the reported drug events. Please refer to Table 28 (Annex 7) for the tabulation of the other actions taken with trastuzumab.

Severity and Nature of Risk

Early breast cancer

Adjuvant treatment:

- BO16348 (HERA)

An overview of the AEs reported under Modified anaphylactic reactions MedDRA basket Version 18.0, based on the reported grades in this study is presented in Table 41.

The majority of AEs reported were of Grade 1 or 2 intensity across all arms (69.1% grade 1 and 29.0% grade 2 in observation arm; 71.0% grade 1 and 25.8% grade 2 in 1-year treatment arm; and 71.0% grade 1 and 26.2% grade 2 in 2-year treatment arm. The majority of the cases reporting Grade 3 under the one year and two-year Herceptin arm were with PT: dyspnea. No other skewed pattern was observed in reporting of Grade 3 and Grade 4 events. Grade 4 cases in Herceptin containing arm consisted of one event each of cardiac arrest (1-year treatment arm) and anaphylactic reaction (2-year treatment arm). One event of hypotension was reported in observation only arm.

Stratified Data

Age ≤50 years:

- Observation only arm: 9.1% (87 out of 959 patients reported a total of 101 AEs). Only Grade 1 (n=80 in 70 patients) and Grade 2 (n=21 in 20 patients) events were reported.
- Herceptin 1-year arm: 23.1% (219/947 patients reported a total of 297 AEs). Majority were Grade 1 (n=211 in 166 patients) and, followed by Grade 2 (n=80 in 72 patients), and six Grade 3 events in 6 patients (dyspnoea [n=2] and one event each of asthma, rash generalized, hypersensitivity and drug hypersensitivity (n=6). No Grade 4 events were reported.
- Herceptin 2-year arm: 28.4% (263/926 patients reported a total of 373 AEs). Majority were Grade 1 (n=270 in 199 patients), followed by Grade 2 (n=92 in 79 patients), Nine Grade 3 events in 8 patients (dyspnoea [n=3] and one event each of cough, hyperventilation, urticaria, chest discomfort, flushing and infusion related reaction, and one Grade 4 event (anaphylactic reaction) were reported.

Age >50 years:

- Observation only arm: 11.8% (93 out of 785 patients reported a total of 116 AEs). Majority were reported as Grade 1 (n=70 in 61 patients) and Grade 2 (n=42 in 38 patients), Three Grade 3 events in 3 patients (asthma [n=2] and one dyspnoea and one Grade 4 event (hypotension) were reported.

- Herceptin 1-year arm: 27.5% (202/735 patients reported a total of 276 events). Majority were Grade 1 (n=196 in 153 patients) and Grade 2 (n=68 in 62 patients). Nine Grade 3 events (in 9 patients (dyspnoea [n=4], hypotension and cough [n=2] each and circulatory collapse [n=1]) and two Grade 4 events (in 2 patients (anaphylactic shock and cardiac arrest) events.
- Herceptin 2-year arm: 32.0% (239/747 patients reported a total of 368 events). Majority were Grade 1 (n=255 in 171 patients) and Grade 2 (n=102 in 90 patients). , Eight Grade 3 events in 8 patients (dyspnoea [n=4], asthma [n=2], rash and anaphylactic reaction). There were no Grade 4 events reported.

Summary: The patients in sub-group >50 years reported higher percentage of patients with AEs compared with the sub-group ≤50 years in all the three arms. For all age groups, majority of the AEs were either Grade 1 or 2 and in line with the unstratified outputs.

Age ≤65 years

- Observation only arm: 9.74% (160 out of 1642 patients reported a total of 191 AEs). Majority were reported as Grade 1 (n=133 in 177 patients) and Grade 2 (n=57 in 52 patients), followed by one Grade 3 (asthma) events. There was no Grade 4 event reported.
- Herceptin 1-year arm: 24.7% (393/1588 patients reported a total of 539 events). Majority were Grade 1 (n=385 in 298 patients) and Grade 2 (n=138 in 125 patients). Thirteen Grade 3 events in 13 patients (dyspnoea [n=5], cough, hypotension [n=2 each], asthma, rash generalized, hypersensitivity and drug hypersensitivity [n=1 each] and two Grade 4 events in two patients (anaphylactic shock and cardiac arrest) were reported.
- Herceptin 2-year arm: 30.1% (477/1583 patients reported a total of 705 events). Majority were Grade 1 (n=502 in 354 patients) and Grade 2 (n=182 in 157 patients). Sixteen Grade 3 events in 15 patients (dyspnoea [n=7], cough, asthma, hyperventilation, rash, urticaria, chest discomfort, flushing, anaphylactic reaction and infusion related reaction [n=1each]) and one Grade 4 (anaphylactic shock) were reported.

Age >65 years

- Observation only arm: 19.6% (20 out of 102 patients reported a total of 26 AEs). Majority were reported as Grade 1 (n=17) and Grade 2 (n=6), followed by Grade 3 (n=2) and Grade 4 (n=1) events.
- Herceptin 1-year arm: 29.8% (28/94 patients reported a total of 34 events). Majority were Grade 1 (n=22) and Grade 2 (n=10), followed by Grade 3 (n=2) events. There was no Grade 4 event reported.
- Herceptin 2-year arm: 27.8% (25/90 patients reported a total of 36 events). Majority were Grade 1 (n=23) and Grade 2 (n=12), followed by Grade 3 (n=1) events. There was no Grade 4 event reported.

Summary: The data for the patients in sub-groups ≤65 years and >65 years do not show a difference compared with the age groups ≤50 years and >50 years; most AEs were reported in the 2-year arm and the majority of the AEs were either Grade 1 or 2. A meaningful interpretation of the data is impacted by low event counts in the sub-group >65 years.

Race:

Observation arm

- Black: 1/6 patients reported 2 events; Caucasian: 144/1453 reported 172 events (Grade 3: 3 events; Grade 4: 1 event); Oriental: 25/218 patients reported 31 events (neither Grade 3 nor Grade 4 events); other: 10/67 patients reported 12 events (neither Grade 3 nor Grade 4 events).

Herceptin 1-year arm

- Black: 3/8 patients reported 3 events (Grade 1:2 events and grade 2: 1 event); Caucasian: 339/1404 patients reported 456 events (Grade 3: 15 events, Grade 4: 2 events); Oriental: 63/213 patients reported 95 events (neither Grade 3 nor Grade 4 events); Other: 16/57 patients reported 19 events (neither Grade 3 nor Grade 4 events).

Herceptin 2-year arm

- Black: 3/5 patients reported 6 events (neither Grade 3 nor Grade 4 events); Caucasian: 395/1397 patients reported 578 events (Grade 3: 16 events, Grade 4: 1 event); Oriental: 82/213 patients reported 127 events (neither Grade 3 nor Grade 4 events); Other: 22/58 patients reported 30 events (Grade 3: 1 event; no Grade 4 event).

Summary: The majority of the patients included in the trials were Caucasian. Across all the race sub-groups, the majority of the events reported were Grade 1 and Grade 2. A meaningful interpretation of the data is impacted by low event counts across other race sub-groups

Neoadjuvant-adjuvant treatment:

- BO22227 (HannaH):

– Table 22 (Annex 7) (IV arm) and Table 23 (Annex 7) (SC arm) show the incidence of ARR events according to severity.

– The severities of the administration-related AEs were similar for both study arms and were distributed amongst Grade 1 through 3. There were no Grade 4 or 5 administration-related AEs for either the Herceptin IV or Herceptin SC treatment arms. The overall incidence of ARRs in the Herceptin IV arm was 37.2% compared with 47.8% in the Herceptin SC arm, i.e., a difference of 10.6%. Following modification of the search parameters (removal of the preferred terms

"hypersensitivity" and "drug hypersensitivity") the overall incidence changes to 29.8% versus 41.1% (IV versus SC, respectively), a difference of 11.3%. This difference in overall incidence was driven by events in the *Skin and subcutaneous tissue disorders* SOC, specifically by erythema (which occurred in 2.7% of patients in the IV arm compared with 7.1% of patients in the SC arm); and by events in the *Respiratory, thoracic and mediastinal disorders* SOC, specifically by cough (which occurred in 8.1% of patients in the IV arm compared with 11.8% of patients in the SC arm). There were six Grade 3 events reported in the Herceptin IV arm (Hypersensitivity/ Drug hypersensitivity (4) and Hypotension (2)) and five Grade 3 events in the Herceptin SC arm (one each for Erythema, Cough, Hypersensitivity, and 2 events for Drug hypersensitivity).

Stratified Data

Events of ARRs in the HannaH trial have been stratified by the following parameters: Age (by categories), Region, and Race.

No stratification by gender: almost exclusively women were included.

Age:

All Body Systems, percentage of patients with at least one AE (and total number of AEs) per age group:

- Age ≤50 years, IV treatment: 45.2% (70 patients, total number of AEs 130).
- Age >50 years, IV treatment: 28.7% (41 patients, total number of AEs 70).
- Age ≤50 years, SC treatment: 51.0% (80 patients, total number of AEs 128).
- Age >50 years, SC treatment: 44.3% (62 patients, total number of AEs 106).

Summary: The patients in sub-group >50 years reported a lower number of AEs compared with the sub-group ≤50 years in both IV and SC arms. For all age-groups, majority of the AEs were either Grade 1 or 2 in line with the unstratified outputs.

Stratification for age-group ≤65 years versus >65 years was not meaningful due to the small number of patients in sub-group >65 years.

Region:

Asia Pacific

- IV: 61.0% (36 patients, total number of AEs 86). All AEs Grade 1 and 2.
- SC: 90.5% (57 patients, total number of AEs 115). All AEs reported as Grade 1 and 2.

Western E.U. incl Canada

- IV: 60.7% (34 patients, total number of AEs 54). All AEs from Grade 1 to 3, most frequently Grade 1 AEs reported (50.0%), Grade 3 minor (3.6%).
- SC: 69.2% (36 patients, total number of AEs 56). All AEs from Grade 1 to 3, most frequently Grade 1 (63.5%), least Grade 3 (5.8%) AEs reported.

South Africa

- IV: 53.3% (8 patients, total number of AEs 14), AEs from Grade 1 to 3, most frequently Grade 1 (53.3), Grade 3 least (6.7%).
- SC: 58.8% (10 patients, total number of AEs 15). All AEs reported as Grade 1 and 2.

South America

- IV: 26.7% (12 patients, total number of AEs 16), all AEs Grade 1 and 2.
- SC: 39.2% (20 patients, total number of AEs 25). All AEs reported as Grade 1 and 2.

Eastern European Area

- IV: 17.1% (21 patients, total number of AEs 30). All AEs from Grade 1 to 3, most frequently Grade 1 (13.8%), Grade 3 least (2.4%).
- SC: 16.7% (19 patients, total number of AEs 23). All AEs from Grade 1 to 3, most frequently Grade 1 (12.3%), Grade 3 least (1.8%).

Summary: Overall, most of the reported events across all sub-groups were Grade 1 and Grade 2. The patients in Asia-Pacific sub-group (both Herceptin IV and Herceptin SC) reported a relatively higher percentage of IRRs.

Race:

Asian:

- IV: 60.7% reported Grade 1 and 2 AEs. No Grade 3 AEs reported.
- SC: 89.1% reported Grade 1 and 2 AEs. No Grade 3 AEs reported.

White:

- IV: 32.7% reported Grade 1 to 3 AEs (2.9% Grade 3 AEs).
- SC: 35.0% reported Grade 1 to 3 AEs (2.5% Grade 3 AEs).

Other:

- IV: 20.7% reported Grade 1 and 2 AEs. No Grade 3 AEs reported.
- SC: 45.5 % reported Grade 1 and 2 AEs. No Grade 3 AEs reported.

Summary: The Asian patients reported a higher number of AEs compared with White and 'Other' race. However, no Grade 3 or greater AE was reported in Asian patients. This finding is consistent with the finding in the regional stratification.

The 5 year follow-up data (last patient last visit 24 January 2017) from this study has now been analyzed and is presented above. No new safety concerns were identified.

- MO22982 (PrefHER)

Results from crossover period SC-IV or IV-SC (N=479 for SC period)

Both Herceptin IV and Herceptin SC:

Most patients reported maximum CTCAE grades during the crossover period of Grade 1 or 2. Mild AEs: 45/479 (9.4%) patients reported 66 events for Herceptin SC period, 20/478 (4.2%) patients reported 25 events for IV period. Moderate AEs: 14/479 (2.9%) patients reported 19 events for Herceptin SC period, 11/478 (2.3%) patients reported 11 events for IV period. Maximum CTCAE Grade 3 events during the crossover period were reported for 5/479 (1.0%) patients (n=5 events) during the Herceptin SC treatment and for 2/478 (0.4%) patients (n=2 events) during IV treatment.

The observed difference between the two formulations results from more mild AEs reported in patients treated with the SC formulation; the AEs primarily contributing to the difference were mild erythema, dyspnoea, and flushing.

There was no meaningful difference between the SC or IV treatment periods in the proportion of patients reporting Grade 3 AEs. A summary of all AEs by maximum CTC Grade is shown in Table 25 of Annex 7.

Continuation period: All ARRs reported during the continuation period were Grade 1 or 2 in severity.

- Study MO28048 (SafeHER)

Overall, the administration-related risks were mainly mild-to-moderate in severity, comprising of Grades 1 and 2 events. The most commonly occurring Grade 1 and Grade 2 AEs were rash cough and erythema. Dyspnoea was the most commonly occurring Grade 3 events. One event each of Anaphylactic shock asthma were reported as Grade 4 event. One event of cardio-respiratory arrest was reported as the Grade 5 event.

Age ≤65 years

- 39.9% (855 out of 2141) patients reported a total of 1251 AEs. Majority were Grade 1 events (n=929 in 629 patients) and Grade 2 (n=288 in 253 patients). There were 30 Grade 3 events in 29 patients, most frequently occurring were dyspnoea (n=4), cough, hypersensitivity and erythema (n=3 each). Anaphylactic shock and cardio-respiratory arrest were reported as Grade 4 and Grade 5 events respectively.

Age >65 years

- 38.2% (165 out of 432) patients reported a total of 243 AEs. Majority were Grade 1 events (n=175 in 130 patients) and Grade 2 (n=57 in 48 patients). There were ten Grade 3 events in 10 patients (dyspnoea [n=6], rash, erythema, respiratory failure and drug hypersensitivity [n=1 each]) and one Grade 4 event of asthma was reported. No Grade 5 events were reported.

Summary: The patients in the sub-group ≤65 years reported more AEs compared with the sub-group >65 years. For all age groups, majority of the AEs were either Grade 1 or 2 in line with the unstratified outputs.

Race

White: 755/1977 (38.2%) patients reported 1097 events (Grade 3: 35 events in 34 patients, Grade 4: two events in two patients and no Grade 5 events).

Black: 19/31 (61.3%) patients reported 30 events (Grade 3: one event, no Grade 4 or 5 events).

Asian: 157/378 (41.5%) patients reported 227 events (Grade 3: 3 events reported in 3 patients, no Grade 4 and Grade 5 events).

Other: 36/89 (40.4%) patients reported 67 events (one Grade 3 and Grade 5 event, and no Grade 4 events).

N/A (per local regulation): 49/89 (55.1%) patients reported 67 events (no Grade 3, 4 or 5 events).

Unknown: 4/9 (44.4%) patients reported 6 events (no Grade 3, 4 or 5 events).

Summary: The majority of the patients included in the trials were White. Across all the race sub-groups, the majority of the events reported were Grade 1 and Grade 2. A meaningful interpretation of the data is impacted by low event counts across other race sub-groups.

Impact on individual patient:

The ARRs are known to occur with the trastuzumab. Serious ARRs to Herceptin IV and Herceptin SC including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress have been reported. Interruption of an IV infusion may help control such symptoms and the infusion may be resumed when symptoms abate. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients who are experiencing dyspnea at

rest due to complications of advanced malignancy or co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with Herceptin.

Since patients are essentially treated in clinical settings under controlled environment equipped to monitor and treat individual patients, the majority of ARRs are identifiable and are clinically manageable.

Risk factors and risk groups:

There are currently no reliable predictors of patients who may or may not be susceptible to administration related reactions to Herceptin. However, the Summary of Product Characteristics (SPC) indicates that patients, who are experiencing dyspnea at rest due to complications of advanced malignancy or co-morbidities, may be at greater risk of severe reactions including fatal outcomes.

Preventability:

Pre-medication may be used to reduce risk of occurrence of ARRs. The MAH describes how ARRs can be managed in the SmPC. For the Herceptin IV administration, these reactions can usually be managed by slowing the infusion or temporarily stopping the infusion until resolution of the symptoms. It should also be noted that Herceptin is also given in combination with chemotherapy on the same (+/- one) day that may also instigate such infusion reactions.

Impact on the benefit-risk balance of the product:

ARRs are clinically manageable with standard therapeutic interventions. The safety profile of Herceptin is well characterized and based on the evaluation of the latest available data the cumulative benefit-risk profile of Herceptin is considered positive and unchanged in all indications.

Public health impact:

No additional public health impact in view of the population treated is anticipated, as monitoring and treatment of ARRs is a routine part of oncology clinical practice. Use outside of controlled environments by non- healthcare professionals (HCPs) is not anticipated.

1.3 OLIGOHYDRAMNIOS

MedDRA Terms:

MedDRA High Level Group Term (HLGT): Neonatal and perinatal conditions; and, MedDRA HLT: Amniotic fluid and cavity disorders of pregnancy NEC and following PTs: Amniotic fluid index, Amniotic fluid index abnormal, Amniotic fluid index decreased, Amniotic fluid index increased, Amniotic fluid volume, Amniotic fluid volume decreased, Amniotic fluid volume increased, Intra-amniotic injection, Vesicoamniotic shunt.

Potential mechanisms:

Bader et al. 2007 hypothesized that Herceptin may have a direct effect on the function of HER2 receptors in the fetal kidney, leading to reduce cell proliferation and restriction of fetal kidney function in vivo. Hypothesis was confirmed in pharmacovigilance surveillance (Drug Safety Report (DSR) 1040470).

Evidence source(s) and strength of evidence:

- Global Safety Database,
- Drug safety reports: DSR #1030381, DSR #1040470 and DSR #10156279.
- Pregnancy registry MotHER [H4621g/GE28099].

Characterization of the risk:

Frequency with 95% CI: Not applicable

Severity and Nature of Risk: Not applicable

Seriousness/ Outcomes:

Oligohydramnios has not been observed in any clinical trials thus far.

Global Safety Database

The information was retrieved cumulatively through August 2018from the MAH's Global Safety Database, utilizing the MedDRA HLGT 'Neonatal and perinatal conditions' and HLT 'Amniotic fluid and cavity disorders of pregnancy NEC' and following 9 PTs -

> Amniotic fluid index, Amniotic fluid index abnormal, Amniotic fluid index decreased, Amniotic fluid index increased, Amniotic fluid volume, Amniotic fluid volume decreased, Amniotic fluid volume increased, Intra-amniotic injection, Vesicoamniotic shunt MedDRA groupings..

A total of 104 AEs (reported in 92 cases) were retrieved (Table 29; Annex 7). Of these, 83(79.8%) AEs were assessed as serious by the reporter and/or the MAH and were distributed amongst 15MedDRA PTs: oligohydramnios n=41 (49.4% of all SAEs in this identified risk group); premature baby n=8 (9.6%), failure to thrive n=10 (12.0%);; neonatal respiratory distress syndrome n=5 6.0%); amniotic fluid volume decreased n=4

(4.8%) each; transient tachypnea of the newborn and death neonatal n=2 (2.4%) each; and thrombocytopenia neonatal, agitation neonatal, meconium aspiration syndrome, neonatal anoxia, neonatal disorder, small for dates baby thrombocytopenia neonatal and umbilical cord abnormality n=1 (1.24%) each. Based on the exposure of Herceptin (until 24 September 2018, the DLP of the latest PBRER of the 2018 PBRER report number 1089226)) in 2,935,329 patients, the crude reporting rate of AEs (reported under the risk of oligohydramnios) is 0.003%

Five AEs (premature baby (n=2), death neonatal, failure to thrive and umbilical cord abnormality), which was 4.8 % of all AEs in this identified risk group, had a fatal outcome. The majority of AEs (n=40) had an unknown or not reported outcome. In six AE reports the event was reported as persisting. A favorable outcome was reported in 36 AEs (34.6% of the 104 total AEs), having recovered/resolved, recovered/resolved with sequelae, or having been recovering/resolving as listed in Table 30 (Annex 7).

Herceptin treatment was withdrawn in response to the AE in 24 (23.1%) of the reported AEs; the action taken in response to the event was unknown in 28 (26.9%) AEs; and the dose was not changed in4 (3.8%) of the AEs, the dose was interrupted for 6 (5.8%) AEs. Further details are illustrated in Table 31 (Annex 7).

A search of the Global Safety Database using the same methodology as described in DSR 1056279 to retrieve any additional cases with the PT 'oligohydramnios' and cases with events within 'Congenital, familial and genetic disorders' SOC, received in the bridging period between the cut-off date of DSR 1056279 (24 April 2013) and 24 September 2014. In the DSR 1056279, four cases of renal impairment co-reported with oligohydraminos had been mentioned. After the cut-off date of the DSR, there was one additional case that reported fetal renal impairment with oligohydramnios.

The five reports of renal impairment co-reported with oligohydraminos are not considered excessive given the total cumulative exposure of Herceptin.

Impact on Individual Patient

Oligohydramnios is associated with risks to fetal development and therefore may have a significant impact on an individual patient. In the post-marketing setting, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving Herceptin. The need to avoid pregnancy during and for 7 months after Herceptin treatment may affect patients' quality of life.

However, patients are likely to face the same restrictions even if Herceptin were not given, since most treatments for breast cancer (chemotherapy, Herceptin, hormone therapy, and radiotherapy) are associated with significant risks to the developing fetus.

Risk factors and risk groups:

There are no reliable indicators of patients who may or may not be at risk.

Preventability:

Current SmPC indicates that treatment with Herceptin only be considered during pregnancy when the potential benefits to the mother outweigh the potential risks to the fetus. Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for at least 7 months after treatment has concluded.

Impact on the benefit-risk balance of the product:

The current labeling documents adequately describe both the risk of oligohydramnios and appropriate risk minimization measures. The MAH has implemented the global enhanced pharmacovigilance (PV) pregnancy program with a purpose to ask for follow-up information at pre-specified time points to collect additional maternal and fetal/infant information on all reports of women exposed to trastuzumab during pregnancy, or within seven months prior to conception, received by the MAH. The review of the latest available data did not lead to any change in the benefit-risk profile for Herceptin.

Public health impact:

Cumulative patient exposure data to Herceptin as of 30 September 2017 was more than 2.6 million. At this time, the number of pregnancies recorded on the Global Safety Database was approximately 467 (given the potential for duplication attributable to the complications of spontaneous reporting). The percentage of pregnancies complicated by oligohydramnios in patients exposed to Herceptin is higher than that seen in the population unexposed to Herceptin; however this does not take into account previous or concurrent chemotherapy or radiotherapy and given the small number of pregnancies reported in the Herceptin exposed population, there is only a very limited, if at all, potential public health impact.

- Pregnancy Registry MotHER [H4621g/GE28099].

MotHER Pregnancy Registry (H4621g/GE28099) was an observational registry sponsored by Roche/Genentech to obtain prospective data on adverse pregnancy complications, including oligohydramnios, as well as pregnancy outcomes, and infant outcomes from pregnancies of women in the United States that have been exposed to a Herceptin-, Perjeta-, or Kadcyla-containing regimen during pregnancy or within 7 months prior to conception. Obstetric and oncologic data are prospectively collected in pregnant women until completion of pregnancy, followed by data related to the infants born to enrolled mothers for 12 months after birth.

As of 31 January 2018 (clinical cut-off date for ADS for 2018), 20 mothers were enrolled in the MotHER Registry (17 mothers exposed to Herceptin-only and 3 mothers exposed

to Perjeta plus Herceptin; no mothers exposed to Kadcyla were enrolled). Fifteen mothers have completed Registry follow-up, 4 mothers discontinued early (including 1 mother who was deemed ineligible for the Registry), and 1 mother (Patient [redacted]) is completed for infant follow-up. Among the 4 mothers who discontinued early, 1 mother discontinued after 6 months of post-delivery follow-up (Patient [redacted]), 1 mother discontinued after 2 months of post-delivery follow-up (Patient [redacted]), 1 mother discontinued after delivery with no additional follow-up (Patient [redacted]), and 1 mother was deemed ineligible for the Registry due to lack of further detail subsequent to self-enrolling into the Registry (Patient [redacted]). This mother was lost to follow-up following self-enrollment.

During pregnancy, 3 mothers experienced oligohydramnios (Patients [redacted]), and 3 mothers experienced polyhydramnios (Patients [redacted]). Oligohydramnios is a recognized and important risk of Herceptin exposure and is listed as an adverse drug reaction in the core data sheet (CDS) for Herceptin and in the boxed warnings of the Herceptin U.S. prescribing information (USPI) as a risk associated with Herceptin use during pregnancy.

The incidence of oligohydramnios observed in this small number of pregnancies is consistent with observations from published literature. However, the rate of polyhydramnios is higher than expected when compared to the literature (1%–2%). Polyhydramnios may be associated with increased perinatal morbidity and mortality (Hamza et al. 2013). Some of the known common causes for polyhydramnios include gestational diabetes, fetal anomalies, smoking, drug exposures (e.g., lithium), and other rare causes (Myhra et al. 1992; Oyebode et al. 2012; Hamza et al. 2013).

In the MotHER Registry, 1 of 3 mothers with polyhydramnios had [redacted] (Patient [redacted]). Two remaining mothers with polyhydramnios had exposure to risk factors during their pregnancy that might be associated with the incidence of polyhydramnios (Patient [redacted] had [redacted], and Patient [redacted] had [redacted] during pregnancy). One of the infants of the mothers with polyhydramnios was reported to have the targeted adverse event (TAE) (these TAEs should be reported regardless of seriousness or severity and include: Oligohydramnios , Hypertensive disorders of pregnancy [e.g., pre-eclampsia, gestational hypertension], Gestational diabetes, intrauterine growth restriction [IUGR], Birth weight below the 10th percentile [i.e., small for gestational age], Delayed renal development) of ”small for gestational age” (Patient [redacted]), and one other infant had events of [redacted] (Patient [redacted]) that were initially reported as non-serious AE but corrected to SAE after additional queries to HCPs regarding these congenital abnormalities. Among the 3 mothers reported with polyhydramnios, Patient [redacted] had an estimated date of conception (EDC) on [redacted], and her last dose of Herceptin was given on [redacted]; polyhydramnios was reported with onset on [redacted] and nearly 7 months after the last dose of Herceptin.

Patient [redacted] had an EDC on [redacted], and her last dose of Herceptin was given on [redacted]; polyhydramnios was reported with onset date of [redacted], [redacted] and nearly 8 months after the last dose of Herceptin. For the remaining mother (Patient [redacted]), despite repeated requests, lack of detail regarding the mother's anticancer treatment and lack of information about the event of polyhydramnios, including sonographic assessments and the polyhydramnios diagnosis date, limit the ability to assess its relationship to Herceptin treatment.

Confounding factors with reported risk for polyhydramnios, such as exposure to [redacted] (Patient [redacted]), [redacted] (Patients [redacted]), and concomitant [redacted] (Patient [redacted]), have been reported in these mothers (Myhra et al. 1992; Oyebode et al. 2012; Hamza et al. 2013). Thus, the higher relative rate of polyhydramnios is interpreted with caution given the confounding risk factors and overall small number of pregnancies in the MotHER Registry. Nevertheless, these events will continue to be monitored per routine pharmacovigilance activities as well as in the Global Enhanced Pharmacovigilance Pregnancy Program for Herceptin, Perjeta, and Kadcyla.

Among the three Perjeta plus Herceptin-exposed mothers in the MotHER Registry (Patients [redacted]), one mother (Patient [redacted]) was deemed ineligible for the registry as mentioned previously. The two other mothers each had a live birth (Patients [redacted]), and no specific SAE or TAE has been reported for these mothers during their pregnancy or post-delivery follow-up provided by the HCP. One mother (Patient [redacted]) has completed the follow-up in the Registry with 2-and 6-month scheduled pediatric visits and an unscheduled pediatric visit at around [redacted] of age for the infant (the birth date was missing for this infant). In addition to the infant's weight, no other information is reported at the pediatric visits, and multiple case report forms have not been reported to the Registry for this mother despite repeated requests. The second Perjeta plus Herceptin-exposed mother (Patient [redacted]) had a live birth and all infant follow-up visits were completed with no reports of congenital defects, life-threatening conditions or serious complications. The third Perjeta plus Herceptin-exposed mother (Patient [redacted]) self-enrolled into the Registry, however lack of further detail resulted in ineligibility of this mother for the Registry and she was lost to follow-up.

As of 31 January 2018, there were known outcomes for 19 pregnancies among 20 mothers enrolled into the Registry, [redacted] in a Herceptin-(only) exposed mother; follow-up is ongoing for an infant of a mother (Patient [redacted]). Overall, gestational age at birth ranged from 33 to 41 weeks. There were three preterm deliveries, one of which was [redacted] that was likely preterm because of [redacted] (Patient [redacted]), one preterm delivery was in a mother with oligohydramnios (Patient [redacted]), and the third preterm delivery was in a mother who experienced pregnancy-induced hypertension (PIH)/preeclampsia (Patient [redacted]).

There was a case of Herceptin-(only) exposed mother (Patient [redacted]) who underwent [redacted] detected through detailed ultrasound imaging at [redacted] weeks of gestation. No information on specific exposure to Herceptin was reported to the Registry for Patient [redacted] despite multiple repeated attempts to obtain data from the HCPs. Patient narratives are provided as part of ADS for 2018.

No unexpected or new safety findings were identified during the evaluation of patients enrolled in the Registry.

The MotHER Registry ADS for 2017 (reporting interval: 1 February 2016 through 31 January 2017) was provided with the application.

Pursuant to the General Advice Letter received from United States Food and Drug Administration (FDA) on 10 August 2017 where the Agency stated that it planned to grant Genentech early fulfillment of the post-marketing commitment for Herceptin only, the MotHER Registry has stopped enrollment for women exposed only to Herceptin during pregnancy or within 7 months prior to conception as of 30 November 2017. The MotHER Registry is closed for eligible women exposed to Perjeta (in combination with Herceptin) or Kadcyla during pregnancy or within 7 months prior to conception. As of 31 January 2018, three mothers exposed to Perjeta plus Herceptin (currently not ongoing in the Registry) and no mothers exposed to Kadcyla have been enrolled in the Registry.

The MAH considers the release of Herceptin from the existing post-marketing commitment appropriate as no new or unexpected safety findings were identified during the latest or any of the previous interim analyses of the Registry. Additionally, maternal and fetal/infant information on all reports of women exposed to Herceptin only (or in combination with Perjeta) including risks of oligohydramnios continues to be monitored per routine pharmacovigilance activities as part of the Global Enhanced Pharmacovigilance Pregnancy Program for Herceptin, Perjeta, and Kadcyla.

Information on Important Potential Risks

1.4 IMMUNOGENICITY/ HYPERSENSITIVITY AND ANAPHYLAXIS OF HERCEPTIN SC

MedDRA term:

Brighton collaboration criteria for anaphylaxis and MedDRA SMQ “Anaphylactic reaction (broad scope)”.

Potential mechanisms:

Immune response to the administration of a protein (IgG). In regard to hypersensitivity, Calogiuri et al. 2009 hypothesize that such reactions (to monoclonal antibodies in general) are attributable to Beta-type reactions: immediate and delayed hypersensitivity; Gamma-type reactions: over-reactions or depression of the immune functions like the

immunodeficient, autoimmune or allergic phenomena; but that other mechanisms such as a specific release of cytokines, might be also involved.

Trastuzumab consists of two antigen-specific sites that bind to the juxtamembrane portion of the extracellular domain of the HER2 receptor and that prevent the activation of its intracellular tyrosine kinase. The remainder of the antibody is human IgG with a conserved fragment crystallizable (Fc) portion that can activate the complement system. Therefore, trastuzumab may cause systemic reactions, which includes hypersensitivity.

Evidence source(s) and strength of evidence:

BO22227 (HannaH), MO22982 (PrefHER) and Halozyme clinical trials.

Characterization of the risk:

Frequency with 95 % CI

Neoadjuvant-adjuvant Treatment in EBC*:*

- BO22227 (HannaH)

At the time of the final analysis and last patient last visit of 24 January 2017, the overall immunogenicity rate for anti- trastuzumab antibodies is 11.1% and 18.0% for patients in the IV and SC arms, respectively. The overall anti-trastuzumab antibody rate at baseline was 5.9 %.

Using the new definition which includes only treatment-induced in the determination of ADA incidence, the overall incidence of anti-trastuzumab antibodies was 10.1% in the Herceptin IV arm and 15.9% in the Herceptin SC arm.

The overall immunogenicity rate for anti-rHuPH20 antibodies is 23.7% for patients in the SC arm. The overall anti-rHuPH20 antibody rate at baseline was 7.46%.

Using the new definition which includes only treatment-induced in the determination of anti-rHuPH20 antibody incidence, the overall incidence of anti-rHuPH20 antibodies was 21.0%. The difference in the overall incidence is due to the exclusion of 9 treatment-unaffected patients that did not have a 4-fold increase in titer post-baseline from their baseline titer or where all post-baseline results were negative, irrespective of the response at baseline.

- MO22982 (PrefHER)

Patients in Cohort 1 (SC SID) only: At baseline and pre-dose Cycle 5, blood samples for rHuPH20 and trastuzumab antibody analyses, respectively, were taken. Serum trastuzumab concentrations were analyzed for these patients to aid in the assessment of immunogenicity.

Of the patients in the safety population with baseline samples available for trastuzumab anti-drug antibody (ADA) testing, 120 patients in the SC SID/IV arm (27 patients de Novo, 93 patients non de Novo) and 121 patients in the IV/SC SID arm (29 patients de Novo, 92 patients non de Novo) were included in the calculation of the baseline trastuzumab ADA rates.

The overall baseline trastuzumab ADA rates were 2.5% (3/120) in the SC SID/IV arm (2 de novo patients and 1 non de novo patient) and 4.1% (5/121) in the IV/SC SID arm (3 de novo patients and 2 non de novo patients). ADA-positive results at baseline among de novo patients were not unexpected as ADA assays utilized statistically derived cut-points designed to result in a small percentage of “false-positives”.

Of the patients in the safety population who received trastuzumab treatment and had post-baseline samples available for trastuzumab anti-drug antibody (ADA) testing, 114 patients in the SC SID/IV arm (25 patients de Novo, 89 patients non de Novo) and 119 patients in the IV/SC SID arm (28 patients de Novo, 91 patients non de Novo) were considered evaluable for an ADA response to trastuzumab.

The overall post-baseline trastuzumab ADA rates were 0% (0/114) in the SC SID/IV arm and 3.4% (4/119) in the IV/SC SID arm. In the IV/SC SID arm, the patients were split 1 de-novo patient and 3 non de-novo patients. The rates were determined using a conservative approach, which considers all patients who were trastuzumab ADA-positive post-baseline regardless of the trastuzumab ADA results at baseline.

Of the 4 patients who were trastuzumab ADA-positive post-baseline, 2 non de-novo patients were trastuzumab ADA-positive at baseline and at Cycle 5 with titers ranging from <1 to 4. The remaining 2 patients (1 de-novo and 1 non de-novo) were trastuzumab ADA-positive at Cycle 5 only with similar titers ranging from <1 to 4. Neutralizing antibodies were not detected in any patients at any time point.

Trastuzumab concentrations $>$50 µg/mL may interfere with the detection of neutralizing anti-trastuzumab antibodies which may result in an under-reporting of neutralizing antibodies while patients are receiving trastuzumab. In both treatment arms, the trastuzumab ADA rates at baseline were higher than the post-baseline rate, which may be due to the increased interference from trastuzumab post-baseline.

ADAs and Injection site reaction (ISRs):

No patients in the SC SID/IV arm were classified as trastuzumab ADA positive. No patients classified as anti-trastuzumab antibody positive post-baseline in the IV/SC SID arm were associated with an ISR. One de Novo patient classified as anti-trastuzumab antibody positive post-baseline in the IV/SC SID arm had an ARR Table 36 (Annex 7). The reported ARR events were AEs of mild local flushing of the skin after SC administration and resolved after 6 to 8 days.

Anti-rHuPH20 Antibodies

Of the patients in the safety population with baseline samples available for rHuPH20 antibody testing, 120 patients in the SC SID/IV arm (27 patients de-novo, 93 patients non de-novo) and 121 patients in the IV/SC SID arm (29 patients de-novo, 92 patients non de-novo) were included in the calculation of the baseline rHuPH20 antibody rates.

The overall baseline rHuPH20 antibody rates were 5.8% (7/120) in the SC SID/IV arm (2 de-novo and 5 non de-novo) and 7.4% (9/121) in the IV/SC SID arm (2 de-novo and 7 non de-novo patients). Three of the patients in the SC SID/IV arm (1 de-novo and 2 non de-novo) were rHuPh20 antibody positive at baseline and predose Cycle 5. The remaining 4 patients (1 de-novo and 3 non de-novo) were rHuPH20 antibody positive only at baseline. Of the 9 patients in the IV/SC SID arm, 7 patients (2 de novo, 5 non de-novo) were rHuPh20 antibody positive at baseline and predose Cycle 5. The remaining 2 non de-novo patients were rHuPH20 antibody positive only at baseline.

Of the safety population who received trastuzumab treatment and had post baseline samples available for rHuPH20 antibody testing, 115 patients in the SC SID/IV arm (26 de novo patients, 89 non de novo patients) and 119 IV/SC SID arm (28 de-novo patients, 91 non de-novo patients) were considered evaluable for an antibody response to rHuPH20 (Table 35; Annex 7).

The overall post baseline rHuPH20 antibody rates were 2.6% (3/115) in the SC SID/IV arm and 7.6% (9/119) in the IV/SC SID arm (Table 37; Annex 7). The rates were determined using a conservative approach, which considers all patients who were rHuPH20 antibody positive post baseline regardless of the rHuPH20 antibody results at baseline.

No additional PK samples for immunogenicity analyses were collected following the Primary analysis

Severity and nature of risk

Neoadjuvant-adjuvant Treatment in EBC:

- BO22227 (HannaH)

Presented in the Table 22 in Annex 7, are listings of terms from the SC arm of BO22227 that have met Brighton collaboration criteria. There were no Herceptin discontinuations or chemotherapy dosage modifications/discontinuations in response to these events.

rHuPH20

There have been very few potential allergic reactions to hyaluronidase, and none that met the Brighton Collaboration Criteria for an anaphylactic reaction with any diagnostic certainty:

One clinical study has been performed to evaluate the sensitivity of healthy volunteer subjects to a single intradermal dose of HYLENEX versus saline (Yocum 2007). Study R04-0851 (ref) was a single-center, double-blind, placebo - and within-subject-controlled study. A total of 100 subjects were injected with 0.1 mL (15 U) of HYLENEX intradermally in the forearm and with 0.1 mL of 0.9% sodium chloride injection USP (saline) in the contralateral forearm (control arm). The study population was 75% female and 79% White, and the mean age was 37 ± 13 years (range 18 to 70 years).

No positive allergic reactions (defined as the occurrence of a wheal with pseudopods within 5 minutes of injection that persisted for at least 20 minutes and was accompanied by localized itching) were observed after the HYLENEX product injection.

In addition, in study HZ2-05-04 AEs representing a possible allergic reaction to HYLENEX/rHuPH20 occurred in a single subject following SC injection of 150 U HYLENEX; the subject experienced erythematous rash on the chest and upper back reported to represent a possible allergic reaction to HYLENEX. The AEs resolved within 10 minutes without intervention. There was no dyspnea, wheezing or pruritus, and no change in vital signs. These data suggest that the subject may have experienced a self-limited allergic reaction to HYLENEX, without anaphylaxis or anaphylactoid reaction. Serological evaluation was not performed.

In two studies involving hyaluronidase/insulin formulations, the following two adverse reactions were reported:

HALO-117-205: An allergic reaction related to aspart-PH20 occurred in a single subject. The subject experienced mild urticaria at the site of the prandial injection.

HALO-117-206: A possible allergic reaction to lispro-PH20 occurred in a single subject and led to premature withdrawal from the study AEs (moderate increased appetite and flushing). Both subjects were tested for rHuPH20 antibodies and were negative at all time points tested. No allergic reactions to HYLENEX have been reported in the post-marketing database (refer to PBRER 2018 report number 1089226).

Seriousness/ outcomes

Neoadjuvant-adjuvant Treatment in EBC

- BO22227 (HannaH)

At the time of final analysis, all patients in the safety population who received Herceptin treatment and had post-baseline samples available for trastuzumab anti-drug antibody (ADA) testing (296 patients in the Herceptin IV arm and 295 patients in the Herceptin SC arm) were considered evaluable for an ADA response to trastuzumab (Table 33; Annex 7).

Of these evaluable patients, a total of 33 patients in the Herceptin IV arm and 53 patients in the Herceptin SC arm had at least one anti-trastuzumab ADA positive post-baseline result (during treatment or in the treatment-free follow-up phase). Using a conservative approach, which considers all patients who were ADA positive post-baseline regardless of the trastuzumab ADA result at baseline, the overall trastuzumab ADA rate was 11.1% (33/296) in the Herceptin IV arm and 18.0% (53/295) in the Herceptin SC arm (Table 33; Annex 7). Neutralizing anti-trastuzumab antibodies (Nabs) were detected in post-baseline (treatment-free) samples from 2 patients in the IV arm and 4 patients in the SC arm.

Using the new definition which includes only treatment-induced and treatment-enhanced patients in the determination of ADA incidence, the overall incidence of anti-trastuzumab antibodies was 10.1% (30/296) in the Herceptin IV arm and 15.9% (47/295) in the Herceptin SC arm (Table 34, Annex 7). Neutralizing anti-trastuzumab antibodies (NAbs) were detected in post-baseline (treatment-free) samples from 2 patients (1 treatment-induced ADA and 1 treatment-enhanced ADA) in the Herceptin IV arm and 3 treatment-induced ADA patients in the Herceptin SC arm. One patient in the SC arm tested positive for NAbs according to the previous definition but was classified as treatment-unaffected ADA, thus reducing the number of patients with NAbs by 1.

In the SC arm, the mean trastuzumab concentrations at both Cycles 8 and 13 were comparable between Nab-negative and Nab-positive patients. In the IV arm, the mean trastuzumab concentration in Nab-positive patients was numerically lower than the mean concentration in Nab-negative patients. However, the concentrations were within the range of concentrations observed in Nab-negative patients. Given the very low number of Nab-positive samples, a definitive conclusion on the effect of neutralizing anti-trastuzumab antibodies on pharmacokinetics cannot be drawn.

The overall immunogenicity rate for anti-rHuPH20 antibodies was 23.7 % (70/295 patients) in the Herceptin SC arm had at least one anti-rHuPH20 antibody positive post-baseline result (during treatment or in the treatment free follow-up phase).

Using a conservative approach, which considers all patients who were anti-rHuPH20 antibody positive post-baseline regardless of the anti rHuPH20 antibody result at baseline, the overall anti-rHuPH20 antibody rate in the Herceptin SC arm was 23.7% (70/295). Neutralizing anti-rHuPH20 antibodies were not detected in any of the patients in the SC arm at any time during the study.

Using the new definition which includes only treatment-induced and treatment-enhanced patients in the determination of anti-rHuPH20 antibody incidence, the overall incidence of anti-rHuPH20 antibodies was 21.0% (62/295) (Table 36, Annex 7). The difference in the overall incidence is due to the exclusion of 9 treatment-unaffected patients that did not have a 4-fold increase in titer post-baseline from their baseline titer or where all post-baseline results were negative, irrespective of the response at baseline.

Nine of 295 evaluable patients (3.1%) treated with Herceptin SC had antibodies to both trastuzumab and rHuPH20.

Neutralizing anti-trastuzumab antibodies (NAbs) were detected in post-baseline samples from 2 patients in the Herceptin IV arm and 4 patients in the Herceptin SC arm.

Impact on individual patient

Exploratory analyses from the HannaH study showed that the occurrence of anti-trastuzumab or anti-rHuPH20 antibodies did not appear to have any clinical consequences with respect to efficacy, safety, or pharmacokinetics.

Risk factors and risk groups:

There are currently no reliable predictors of patients who may or may not develop anti-therapeutic antibodies. However, current professional labeling indicates that patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, may be at greater risk of severe reactions. These patients should not be treated with Herceptin.

Preventability:

Not applicable

Impact on the benefit-risk balance of the product:

The final analysis from study BO22227 (HannaH) confirmed that no correlation has been identified between the trastuzumab ADA status and trastuzumab pharmacokinetics, efficacy, or safety. The benefit-risk profile of Herceptin remains unchanged.

Public health impact:

None

1.5 SHORT-TERM SAFETY OF HERCEPTIN SC COMPARED TO HERCEPTIN IV

MedDRA terms:

Comparison of all AEs from post-marketing source with a latency of onset ≤1 year from first dose of Herceptin at the level of SOC was performed.

Potential mechanisms:

Higher absolute dose intensity of Herceptin SC versus Herceptin IV.

Evidence source(s) and strength of evidence:

Studies BO22227 (HannaH), MO22982 (PrefHER), MO28048 (SafeHer) and Global Safety Database.

Characterization of the risk:

Frequency with 95% CI: Not available

Severity and nature of risk

- BO22227 (HannaH)

At the time of final analysis, the incidence of severe (Grade ⩾3) AEs was comparable between treatment arms (53.7% [160/298] in the Herceptin IV arm and 53.2% [158/297] in the Herceptin SC arm).

- MO22982 (PrefHER)

Results from crossover period SC-IV or IV-SC (N=479).

All SAEs were considered unrelated to the treatment with Herceptin and the majority for both Herceptin IV and SC were Grade 3 AE's.

Any differences in AE rates between Herceptin IV and Herceptin SC were due to Grade 1 or 2 AEs – primarily ISRs - and were not clinically relevant.

- MO28048 (SafeHER)

Five Grade 5 AEs (death) were reported during the treatment period.

Overall, 67 patients (2.6%) reported 74 Grade 4 (life-threatening) AEs (52 patients [2.8%] with 59 events in Cohort A and 15 [2.1%] with 15 events in Cohort B). Most of the Grade 4 AEs were blood and lymphatic system disorders (reported in 46 patients [1.8%], with neutropenia in 24 patients [0.9%] and febrile neutropenia in 18 [0.7%]).

A similar pattern was observed in the case of Grade 3 AEs (severe), with 21.5% patients overall (22.3% in Cohort A and 19.2% in Cohort B) reporting this grade of AE. Thus, the most frequently reported SOC was blood and lymphatic system disorders (145 patients [5.6%] with 203 events). Other frequently reported SOCs with Grade 3 AEs were gastrointestinal disorders (74 patients [2.9%] with 96 events), vascular disorders (69 patients [2.7%] with 88 events), and infections and infestations (69 patients [2.7%] with 81 events). The most frequently reported individual Grade 3 events were neutropenia and febrile neutropenia (69 patients [2.7%] and 43 patients [1.7%], respectively).

Seriousness/outcomes:

Neoadjuvant-adjuvant Treatment in Early Breast Cancer:

- BO22227 (HannaH)

Overall, there were 15.1% (45/298) of patients in the Herceptin IV arm who experienced an SAE compared with 21.9% (65/297) in the Herceptin SC arm. During the treatment-free follow-up phase, the SAE incidence rates were low in both treatment arms (5/298 patients [1.7%] in the Herceptin IV arm and 2/297 patients [0.7%] in the Herceptin SC arm had experienced seven SAEs in total). The difference between treatment arms driven by an imbalance during the treatment period is described in the Update CSR (Report No. 1057070, September 2013). No other pattern in types of events, affected SOCs, or latency accounted for the imbalance.

Nine fatal AEs were reported andfour occurred during the neoadjuvant treatment phase (acute pneumonia in the Herceptin IV arm and myocardial infarction, sudden death, and septic shock in the Herceptin SC arm). The remaining 5 patients died due to reportable AEs that occurred during the treatment-free follow-up phase (4 in the Herceptin IV treatment arm 1 with Grade 3 myeloid leukemia leading to death of patient, death due to an unknown cause, Grade 5 myocardial infarction leading to death on the same day and emphysema leading to the death of the patient on the same day; in the Herceptin SC treatment arm there was 1 case due to Grade 3 endometrial cancer). Refer to Section 1.4 for immunogenicity data from Study BO22227.

- MO22982 (PrefHER)

Results from crossover period SC-IV or IV-SC (479 patients Herceptin SC and 478 patients received Herceptin IV). The total number of AEs was higher with Herceptin SC (300/479 [62.6%] of patients reported 913 AEs) compared with Herceptin IV (258/478 [54.0%] of patients reported 581 AEs). The difference is mainly due to the occurrence of Injection Site Reactions which is specific for the SC phase. After excluding the 186 ISRs the rate of AE's is similar for both Herceptin IV and SC (57.4% versus. 54.0%). Refer to Table 39 (Annex 7).

The number of SAE during the crossover period was low and balanced between Herceptin IV and Herceptin SC: 4 for SC and 5 for IV were reported. All SAEs were considered unrelated to the treatment with Herceptin and the majority were grade 3 AEs. No deaths occurred. Refer to Table 40 (Annex 7).

- MO28048 (SafeHER)

Safety and tolerability results, including in lower weight patients, were consistent with the known safety profile for Herceptin IV and SC. Please refer to Table 41 (Annex 7).

Global Safety Database

The following assessment is based on the number of AEs, SAEs, and fatal events, reported in the global safety database (cut-off date of 31 August 2017) as a proportion of the total events reported (Refer to Table 42 (Annex 7).

For the majority of SOCs, the number of AEs for Herceptin SC is less than the number of AEs for Herceptin IV. A higher percentage (≤ 1%) of AEs, SAEs, or both, were reported for the following SOCs for Herceptin SC compared to Herceptin IV:

General disorders and administration site conditions:

A comparable percentage of overall AEs with trastuzumab SC versus. trastuzumab IV (19.8% versus. 17.3%), however, SAEs were reported with similar frequency with both trastuzumab SC and trastuzumab IV (13.3% versus. 13.8%).

Infections and Infestations:

A comparable percentage of overall AEs and SAEs, respectively with trastuzumab SC versus. trastuzumab IV (6.1% versus. 4.5%) and (7.6% versus. 5.6%).

Musculoskeletal and connective tissue disorders:

A higher percentage of overall AEs and SAEs, respectively with trastuzumab SC versus. trastuzumab IV (11.9% versus. 6.4%) and (6.1% versus. 2.8%).

Skin and subcutaneous tissue disorders:

A comparable percentage of overall AEs with trastuzumab SC versus trastuzumab IV (9.9% versus. 8.9%), however, SAEs were reported less frequently with trastuzumab SC versus trastuzumab IV (3.3% versus. 4.6%).

Impact on individual patient:

Herceptin SC is injected as a fixed dose formulation (600 mg), this may potentially lead to relative overdose in patients with low body mass index and may thence have propensity for increased adverse effects. Currently, the data suggesting direct impact on individual patient is limited.

Risk factors and risk groups:

Patients receiving the higher absolute dose intensity of Herceptin SC

Preventability:

Not applicable

Impact on the benefit-risk balance of the product:

The review of the latest available data did not lead to any change in the benefit-risk profile of Herceptin.

Public health impact:

None

SVII.3.2. Presentation of the Missing Information

1 Long-term safety of Herceptin SC compared to Herceptin IV

Evidence source:

Patient treated with the Herceptin SC receive a higher cumulative dose of Herceptin compared to Herceptin IV. At the time of Herceptin SC extension application, the evidence if this higher cumulative dose could lead to more adverse effects was limited and was expected to be observed with longer follow-up.

Long-term safety of Herceptin SC compared to Herceptin IV will be evaluated from the long-term safety follow-up for Study BO22227 (HannaH) and Study MO28048 (SafeHER). Patients will be followed for 5 years post treatment and undergo echocardiogram (ECHO) or multi gated acquisition scan (MUGA) scans every 6 months until the 2-year timepoint, then yearly until the 5-year timepoint. The 5-year follow-up CSR would provide long-term data. Study BO22227 5 year follow up data and final CSR are now available.

- BO22227 (HannaH)

Long-term safety of Herceptin SC and the safety profile of the proportionally higher dose of Herceptin SC in lower weight patients (fixed dose of 600 mg Herceptin SC irrespective of the patient's body weight) was considered to be important missing information.

This was evaluated from the long-term safety follow-up for Study BO22227 (HannaH). Patients were followed for 5 years post treatment and underwent ECHO or MUGA scans every 6 months until the 2 year time-point, then yearly until the 5 year time-point. The 5-year follow-up data as presented in the Final CSR provided the long-term data (data collected after median follow-up of 71 months). The overall safety profile of Herceptin SC continues to be consistent with the known safety profile for Herceptin IV. No new safety signals were observed, and similar incidences of all AEs were observed in the lower weight patient quartiles in the Herceptin SC treatment arm compared with the Herceptin IV treatment arm.

2 Safety of Docetaxel 75 mg/m2 versus 100 mg/m2

Evidence source:

In trials with Herceptin SC in early breast cancer, concomitant docetaxel was administered at 75 mg/m^2 compared to 100 mg/m^2 with Herceptin IV.

Study BO22227 included concomitant usage of Herceptin with docetaxel 75 mg/m^2; therefore, the concomitant use of Herceptin with docetaxel 100 mg/m^2 is considered to be missing information. The MAH committed to present an annual analysis of the safety profile of Herceptin when used concomitantly with docetaxel 75 mg/m^2 versus usage with docetaxel 100 mg/m^2 within scheduled PSURs. The first analysis was submitted to regulatory authorities in 2014.

The Study BO22227 (HannaH) was completed and the data from final study results concluded that the overall safety profile of Herceptin in combination with docetaxel 75 mg/m^2 continues to be consistent with the known safety profile. No new safety signals were observed.

The data from the Roche Global safety database was reviewed to compare the safety of Herceptin + docetaxel 75 mg/m^2 and Herceptin+docetaxel 100 mg/m^2. A meaningful comparison between the two dosing regimens of docetaxel with the SC Herceptin

formulation for breast cancer is impacted by the small number of reported cases, especially with the 100 mg/m^2 regimen.

The MAH does not have access to the data regarding exposure to the two different docetaxel regimens: the increase in docetaxel dosage from 75 mg/m2 to 100 mg/m2 is at prescribers' discretion and may vary across clinical practice. The lower reporting proportion of cases with the 100mg/m2 regimen is suggestive that the use of this regimen is too limited to support further analysis or provide any conclusive evidence.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 44 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Cardiac dysfunction • Administration-Related Reactions Oligohydramnios
Important potential risks	• Immunogenicity/ Hypersensitivity and Anaphylaxis of Herceptin SC • Short term safety of Herceptin SC compared to Herceptin IV
Missing information	• Long term safety of Herceptin SC compared to Herceptin IV • Safety of 75mg/m2 v 100mg/m2 docetaxel dose

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires (guided questionnaires):

- Medication Error (IV versus SC)

  Kadcyla administration instead of Herceptin

  IV administration of SC formulation or SC administration of IV formulation

- Oligohydramnios:

  The purpose of these guided questionnaires is to collect information on pregnancies and pregnancy outcomes. Please see Annex 4 of the RMP for details.

  Global enhanced PV pregnancy program is effective and being implemented globally including the E.U., since 1 January 2015 for the identified risk of oligohydramnios.

Other forms of routine pharmacovigilance activities:

Safety of 75 mg/m^2 versus 100 mg/m^2 docetaxel dose: Annual review and analysis of data from the global safety database for submission with the PBRER/PSUR.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Safety Concern: Cardiac dysfunction

BO29159 (MetaPHER) has recently been completed. Herceptin SC in combination with Perjeta IV and docetaxel chemotherapy has a comparable safety profile to that of Perjeta and Herceptin IV formulations in combination with chemotherapy. No new or unexpected toxicities were observed for the safety concern of cardiac dysfunction other than those that are known for agents that target the HER2 family of receptors

No additional PV activity for the safety concern of cardiac dysfunction will be conducted Therefore, no further information from this trial will be presented in the future updates to this RMP. The final CSR for this trial will be submitted to the EMA with this Variation application EMEA/H/C/278/II/XXX, prior to the agreed Agency deadline of 31 December 2019.

Table 45 PASS BO29159 (MetaPHER)*

Study/activity short name and title: BO29159 (MetaPHER) A multicenter, open-label, single-arm study of Herceptin SC in combination with Perjeta and Docetaxel in first-line treatment of patients with HER2-positive advanced breast cancer (metastatic or locally recurrent).
Rationale and Study Objectives: *Primary objective:* To evaluate the safety and tolerability of Herceptin SC in combination with Perjeta plus docetaxel in patients with HER2-positive advanced (metastatic or locally recurrent) breast cancer. *Secondary Objectives* The secondary objectives for this study are to evaluate Herceptin SC in combination with Perjeta IV plus docetaxel with respect to: • Efficacy parameters (see protocol) • Progression-free survival (PFS) • Overall Survival (OS) • Objective response rate (ORR) • Incidence of anti-Herceptin and anti-rHuPH20 antibody formation
Study design: An open-label, single-arm, multicenter, Phase IIIb study
Study populations: 400 patients are planned to be enrolled into the study at approximately 110 centers worldwide.
Milestones: Study Start – FPI- 2015 LPI- 2016 Final Report- By 31 December 2019
Note: The MetaPHER final CSR will be submitted to the EMA prior to the agency agreed deadline of 31 December 2019 together with EU RMP version 21.0. FPI=first patient in; HER2= human epidermal growth factor receptor 2; IV=intravenous; LPI=last patient in, ORR=objective response rate; OS= overall survival; PFS=progression-free survival; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous.

Safety concern: Oligohydramnios

As of 14 February 2019, the MAH has been released from all commitments regarding the MotHER Registry in the U.S. and the E.U. and hence the MotHER Registry (H4621g/GE28099) is now closed to all patients exposed to Herceptin, Perjeta (in combination with Herceptin) or Kadcyla. No further additional pharmacovigilance activity will be conducted within the MotHER Registry for the safety concern of oligohydramnios. However, maternal and fetal/infant information on all reports of women exposed to Herceptin only (or in combination with Perjeta) including risks of oligohydramnios will continue to be monitored per routine pharmacovigilance activities as part of the Global Enhanced Pharmacovigilance Pregnancy Program for Herceptin, Perjeta, and Kadcyla.

Safety Concern: Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin SC

- ADA and Immunogenicity data from MO28048 (SafeHER) final CSR. Details of this study are presented in Table 46.
- BO29159 (MetaPHER). Details of this study are presented in Table 45.
- Monitoring of ADA antibody formation (to trastuzumab and rHuPH20) in the extension of the follow-up phase of Study BO22227 (HannaH). Details of the HannaH study are presented in the HannaH Final CSR submitted to the EMA in December 2017 and FDA in April 2018.

Safety Concern: Short term safety of Herceptin SC compared to Herceptin IV

This Safety concern represents an important potential risk.

- MO28048 (SafeHER) Annual Report and Primary CSR (following completion of treatment). The details of this study are presented in the Table 46 below.
- BO22227 (HannaH) 5-year follow-up CSR submitted December 2017.

Table 46: MO28048 (SafeHER)

Study/activity short name and title: MO28048 (SafeHER) A Phase III prospective, two cohort non-randomized, multicentre, multinational, open label study to assess the safety of assisted- and self-administered SC Herceptin as adjuvant therapy in patients with operable HER2-positiveEBC.
Rationale and Study Objectives: Primary Objective To assess the overall safety and tolerability of SC Herceptin in HER2-positive EBC patients with assisted administration using a conventional syringe and needle (vial formulation) and with assisted administration with or without self-administration using a SID in patients willing and judged competent to do so. Exploratory Objective To assess the immunogenicity of Herceptin and recombinant human hyaluronidase (rHuPH20) in a subset of patients receiving Herceptin SC using the SID (Cohort B) at select sites.
Study design: Phase III, prospective, two-cohort, non-randomized, multi-centre, multinational, open label study.
Study populations: Patients with newly diagnosed HER2-positive (immunohistochemistry [IHC] 3+ or HER2-positive in situ hybridization [ISH]) clinical stage I (T1, N0, M0) to IIIC (any T, N3, M0) EBC who are eligible for treatment with Herceptin SC. Patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low risk node negative tumours ≤ 1.0 cm, elderly patients (>65 years of age) or patients who refuse chemotherapy, will also be eligible to participate in the study, but their enrolment will be limited to approximately 10% of the total study population.

Milestones: Study Start – FVFP-17 May 2012 Interim Analyses- Annual reports submitted with PBRER/PSUR Study Finish- Ongoing Final Report-2020
EBC=early breast cancer; FVFP=first visit of first patients; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=in situ hybridization; PBRER= periodic benefit risk evaluation report; PSUR=periodic safety update report SC=subcutaneous; SID=single-use injection device.

Safety Concern: Long Term Safety of Herceptin SC Compared to Herceptin IV

This Safety concern represents 'Missing information'.

- Extension of follow-up phase of study BO22227 (HannaH) to 5 years. BO22227 annual reports BO22227, 2-year and 5-year follow-up CSR. The final Hannah 5 year follow-up analysis and associated CSR are complete.
- Extension of follow-up phase of Study MO28048 (SafeHER) to 5 years. 5-year follow-up CSR will include analysis of long-term safety data. The details of the mentioned studies are presented in Table 46.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 47 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
NA	NA	NA	NA	NA
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
NA	NA	NA	NA	NA
Category 3 - Required additional pharmacovigilance				
BO29159 (MetaPHER) A multicenter, open-label, single-arm study of Herceptin SC in combination with Perjeta and Docetaxel in first-line treatment of patients with HER2-positive advanced breast cancer (metastatic or locally recurrent) Ongoing	*Primary objective:* To evaluate the safety and tolerability of Herceptin SC in combination with Perjeta plus docetaxel in patients with HER2-positive advanced (metastatic or locally recurrent) breast cancer. *Secondary Objectives* The secondary objectives for this study are to evaluate Herceptin SC in combination with Perjeta IV plus docetaxel with respect to: • Efficacy parameters (see protocol) • Progression-free survival (PFS) • Overall Survival (OS) • Objective response rate (ORR) • Incidence of anti-Herceptin and anti-rHuPH20 antibody formation	• Immunogenicity/Hypersensitivity and Anaphylaxis Herceptin SC • Cardiac dysfunction	Study Start LPI	2015 2016 Interim report submitted on December 2017, in support of a Type II variation application for Perjeta (EMEA/H/C/2547/II /0035) to update the Perjeta SmPC to allow administration of Perjeta with Herceptin SC. Commission Decision issued on 30 April 2018. Final Report:2019: The final CSR will be submitted to

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
				EMA via a Type II variation (EMEA/H/C/278/II/XX)
MO28048 (SafeHER): A Phase III prospective, two cohort non-randomized, multicentre, multinational, open label study to assess the safety of assisted- and self-administered subcutaneous Herceptin as adjuvant therapy in patients with operable HER2-positive early breast cancer [SafeHer Study]. Ongoing	*Primary Objective* The primary objective of this study is to assess the overall safety and tolerability of subcutaneous (SC) Herceptin in HER2-positive early breast cancer (EBC) patients with assisted administration using a conventional syringe and needle (vial formulation) and with assisted administration with or without self-administration using a single-use injection device (SID). *Exploratory Objectives* To assess the immunogenicity of Herceptin and recombinant human hyaluronidase (rHuPH20) in a subset of patients receiving Herceptin SC using the SID (Cohort B) at select sites.	• Immunogenicity/Hypersensitivity and anaphylaxis of Herceptin SC • Short term safety of Herceptin SC compared to Herceptin IV	Interim Analyses	Annual reports submitted with PBRER/PSUR
			Final Report	2020

ADS= Annual Data Summary; ASR= Annual Safety Report ; CHF=congestive heart failure; CSR=Clinical Study Report; EMA= European Medicines Agency; EBC= early breast cancer; EFS=event-free survival; FDA= U.S. Food and Drug Administration; HER2= Human Epidermal Growth Factor Receptor 2; IUGR= intrauterine growth restriction; IV=intravenous; LVEF=Left Ventricular Ejection Fraction; NYHA=New York Heart Association; OS=Overall Survival; ORR=Objective response rate ; PV=Pharmacovigilance ; PFS=Progression-free; PSUR= Periodic Safety Update Report; PBRER= Periodic Benefit Risk Evaluation Report; SC=subcutaneous; SID=single-use injection device; SNP= single nucleotide polymorphisms ; TTR=time to response

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Note: The MetaPHER final CSR will be submitted to the EMA in November 2019 together with EU RMP version 21.0. This study is retained as ongoing in the present EU RMP update. The study will be moved to completed studies after CHMP approval in subsequent RMP updates.				

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

IV.1 PLANNED AND ONGOING POST-AUTHORIZATION IMPOSED EFFICACY STUDIES THAT ARE CONDITIONS OF THE MARKETING AUTHORISATION OR THAT ARE SPECIFIC OBLIGATIONS

Not applicable. Herceptin is advanced in clinical development. No post authorization efficacy studies are planned or needed to investigate efficacy in the target population.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

RISK MINIMIZATION PLAN

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 48 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Cardiac dysfunction	**Routine risk communication:** SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Monitoring to identify patients who develop cardiac dysfunction and clinical recommendation algorithm to deal with LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.4 of SmPC. **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.
Administration-related reactions	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk**: Guidance on observation period after administration has been adequately captured in Section 4.2 of E.U. SmPC. **Other risk minimization measures beyond the Product Information**: Pack Size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.

Safety concern	Routine risk minimization activities
Oligohydramnios	**Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** If a pregnant woman is treated with Herceptin or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable. This has been captured in Section 4.6 of E.U. SmPC. **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.
Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin SC	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous vial) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.
Short term safety of Herceptin SC compared to Herceptin IV	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous vial) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.
Long term safety of Herceptin SC compared to Herceptin IV	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous vial) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.
Safety of docetaxel 75 mg/m^2 versus 100 mg/m^2	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.
LVEF=left ventricular ejection fraction; SmPC=summary of product characteristics;	

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

None

Rationale for proposing to remove additional risk minimization measures

Direct Health Care Professional Communication (DHCP) for increased risk of cardiac dysfunction has been removed as additional risk minimization measure considering a report of the survey findings was submitted to the EMA in January 2018 and was assessed by PRAC under PAM procedure EMEA/H/C/000278/LEG100. Confirmation of CHMP adoption of PAM fulfilment was issued on 29 April 2018.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 49 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Cardiac dysfunction	**Routine risk communication:** SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Monitoring to identify patients who develop cardiac dysfunction and clinical recommendation algorithm to deal with LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.4 of SmPC **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** BO29159 (MetaPHER) has recently been completed. No additional PV activity for the safety concern of cardiac dysfunction will be conducted through this trial. Final CSR shall be submitted with EU RMP v 21.0
Administration-Related Reactions (ARRs)	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk**: Guidance on observation period	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	after administration has been adequately captured in Section 4.2 of E.U. SmPC. **Other risk minimization measures beyond the Product Information**: Pack Size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. **Additional risk minimization measures:** None	
Oligohydramnios	**Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** If a pregnant woman is treated with Herceptin or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable. This has been captured in Section 4.6 of E.U. SmPC. **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: (**Guided questionnaire for pregnancy related adverse events) Please see Annex 4 of the RMP for details Global enhanced PV pregnancy program is effective and being implemented globally including the EU, since 1 January 2015 for the identified risk of oligohydramnios **Additional pharmacovigilance activities: None** H4621g/GE28099 (MotHER Pregnancy Registry): No further additional pharmacovigilance activity will be conducted within the MotHER Pregnancy Registry
Immunogenicity/ Hypersensitivity and Anaphylaxis of Herceptin SC	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous (SC vial) E.U. SmPC) **Routine risk minimization**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	activities recommending specific clinical measures to address the risk: None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial **Legal Status:** Herceptin is a prescription only medicine. **Additional risk minimization measures**: None	**Additional pharmacovigilance activities:** BO29159 (MetaPHER) has recently been completed. No additional PV activity for the safety concern of Immunogenicity/ Hypersensitivity and Anaphylaxis of Herceptin SC will be conducted through this trial. Final CSR shall be submitted along with EU RMP v21.0 Study MO28048 (SafeHER) Monitoring of ADA antibody formation (to trastuzumab and rHuPH20) in the extension of the follow-up phase of Study BO22227 (HannaH)- final 5year follow-up analysis has been completed.
Short term safety of Herceptin SC compared to Herceptin IV	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous (SC vial) E.U. SmPC) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial **Legal Status:** Herceptin is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study MO28048 (SafeHER)
Long term safety of Herceptin SC compared to Herceptin IV	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous (SC vial) E.U. SmPC) **Routine risk minimization**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	activities recommending specific clinical measures to address the risk: None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial **Legal Status:** Herceptin is a prescription only medicine **Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** Study BO22227 (HannaH)- final 5year follow-up analysis has been completed Study MO28048 (SafeHER)
Safety of 75mg/m2 v 100mg/m2 docetaxel dose	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

ADA=anti-drug antibody; ADS=annual data summary; EMA= European Medicines Agency; FDA=Food and Drug Administration; LVEF=left ventricular ejection fraction; rHuPH20= recombinant human hyaluronidase PH20; RMP=risk management plan; SC= subcutaneous; SmPC=summary of product characteristics.

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR HERCEPTIN

This is a summary of the risk management plan (RMP) for Herceptin®. The RMP details important risks of Herceptin®, how these risks can be minimized, and how more information will be obtained about Herceptin® risks and uncertainties (missing information).

Herceptin®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals (HCP) and patients on how Herceptin® should be used.

This summary of the RMP for Herceptin® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Herceptin® RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Herceptin® is authorized for metastatic breast cancer (MBC), early breast cancer (EBC) and metastatic gastric cancer (MGC) (see SmPC for the full indication). It contains Trastuzumab as the active substance and it is given by intravenous and subcutaneous.

Further information about the evaluation of Herceptin® benefits can be found in Herceptin® EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000278/human_med_000818.jsp&mid=WC0b01ac058001d124

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Herceptin®, together with measures to minimize such risks and the proposed studies for learning more about Herceptin® risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Herceptin®, these measures are supplemented with *additional risk minimization* measures mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed: including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of Herceptin® are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Herceptin®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Cardiac dysfunction Administration-Related Reactions (ARRs) Oligohydramnios
Important potential risks	Immunogenicity/ Hypersensitivity and Anaphylaxis of Herceptin SC Short term safety of Herceptin SC compared to Herceptin IV
Missing information	Long term safety of Herceptin SC compared to Herceptin IV Safety of 75mg/m2 v 100mg/m2 docetaxel dose

II.B Summary of Important Risks

Important Identified Risk	
Cardiac dysfunction	
Evidence for linking the risk to the medicine	MBC: M77001 and BO16216. EBC: Joint Analysis (NSABP B-31 and NCCTG N9831), BCIRG 006 (H2296s)/GO00773, BO16348, MO16432, BO22227, MO22982, MO28048 GC: BO18255. QTc-study H4613g (HerQLes). Global Safety Database
Risk factors and risk groups	Patient with Early Breast Cancer (EBC)
Risk minimization measures	**Routine risk communication:** SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Monitoring to identify patients who develop cardiac dysfunction and clinical recommendation algorithm to deal with LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.4 of SmPC **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BO29159 (MetaPHER) See section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk	
Administration-Related Reactions (ARRs)	
Evidence for linking the risk to the medicine	EBC: Studies BO16348, BO22227, MO22982, and MO28048. Global Safety Database. Drug Safety Reports, DSR 1036301 dated 12 December 2009, DSR 1056779 dated 27 June 2013 and DSR 1060413 dated 15 May 2014
Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not be susceptible to administration related reactions to Herceptin. However, the SPC indicates that patients, who are experiencing dyspnea at rest due to complications of advanced malignancy or co-morbidities, may be at greater risk of severe reactions including fatal outcomes.
Risk minimization measures	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk**: Guidance on observation period after administration has been adequately captured in Section 4.2 of E.U. SmPC. **Other risk minimization measures beyond the Product Information**: Pack Size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. *Additional risk minimization measures:* No risk minimization measures
Additional pharmacovigilance activities	There are no additional pharmacovigilance activities

Important Identified Risk	
Oligohydramnios	
Evidence for linking the risk to the medicine	Global Safety Database, Drug safety reports #1030381, 1040470 and 10156279. Pregnancy registry MotHER [H4621g/GE28099 is closed].
Risk factors and risk groups	There are no reliable indicators of patients who may or may not be at risk
Risk minimization measures	**Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** If a pregnant woman is treated with Herceptin or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable. This has been captured in Section 4.6 of E.U. SmPC. **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine *Additional risk minimization measures:* No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: H4621g/GE28099 (MotHER Pregnancy Registry) is closed and no further additional pharmacovigilance activity will be conducted. -

Important Potential Risk	
Immunogenicity/ Hypersensitivity and Anaphylaxis of Herceptin SC	
Evidence for linking the risk to the medicine	BO22227 (HannaH), MO22982 (PrefHER) and Halozyme clinical trials.
Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not develop anti-therapeutic antibodies. However, current professional labelling indicates that patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, may be at greater risk of severe reactions. These patients should not be treated with Herceptin.
Risk minimization measures	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous vial) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. *Additional risk minimization measures:* No risk minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** BO29159 (MetaPHER) has recently been completed. No additional PV activity for the safety concern of Immunogenicity/ Hypersensitivity and Anaphylaxis of Herceptin SC will be conducted through this trial. Final CSR shall be submitted with EU RMP v21.0MO28048 (SafeHER) Monitoring of ADA antibody formation (to trastuzumab and rHuPH20) in the extension of the follow-up phase of study BO22227 (HannaH). The Hannah 5 year follow-up CSR has been completed and was submitted to the EMA in December 2017. See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risk	
Short term safety of Herceptin SC compared to Herceptin IV	
Evidence for linking the risk to the medicine	Studies BO22227, MO22982,MO28048 (SafeHer) and Global Safety Database
Risk factors and risk groups	Patients receiving the higher absolute dose intensity of Herceptin SC.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 Undesirable effects (Subcutaneous vial) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. Additional risk minimization measures: No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: MO28048 (SafeHER) See section II.C of this summary for an overview of the post-authorization development plan.

Important Missing Information	
Long term safety of Herceptin SC compared to Herceptin IV	
Evidence for linking the risk to the medicine	Patient treated with the Herceptin SC receive a higher cumulative dose of Herceptin compared to Herceptin IV. It is not yet known whether this higher cumulative dose may lead to more adverse effects which can only be observed after a longer follow-up.
Risk factors and risk groups	As above
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 Undesirable effects (Subcutaneous vial) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. Additional risk minimization measures: No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: BO22227 (HannaH)-completed; Final CSR was submitted to the EMA in 2017. MO28048 (SafeHER) See section II.C of this summary for an overview of the post-authorization development plan.

Important Missing Information	
Safety of 75mg/m2 v 100mg/m2 docetaxel dose	
Evidence for linking the risk to the medicine	In trials with Herceptin SC in early breast cancer, concomitant docetaxel was administered at 75 mg/m^2 compared to 100 mg/m^2 with Herceptin IV.
Risk factors and risk groups	As above
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 Posology and method of administration. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. Additional risk minimization measures: No risk minimization measures
Additional pharmacovigilance activities	None

II.C Post-Authorization Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorization

Not applicable.

II.C.2 Other Studies in Post-Authorization Development Plan

BO29159 (MetaPHER) has recently been completed and final CSR shall be submitted along with EU RMP v 21.0. No additional PV activity for the safety concern of Immunogenicity/Hypersensitivity and Anaphylaxis and cardiac dysfunction of Herceptin SC will be conducted through this trial.

- Study short name: MO28048 (SafeHER)

Purpose of the study:

Primary Objective**:**

The primary objective of this study is to assess the overall safety and tolerability of subcutaneous (SC) Herceptin in HER2-positive early breast cancer (EBC) patients with assisted administration using a conventional syringe and needle (vial formulation) and with assisted administration with or without self-administration using a single-use injection device (SID).

Exploratory Objectives:

To assess the immunogenicity of Herceptin and recombinant human hyaluronidase (rHuPH20) in a subset of patients receiving Herceptin SC using the SID (Cohort B) at select sites.

ANNEX 1:

EUDRAVIGILANCE INTERFACE

ANNEX 1 – EUDRAVIGILANCE INTERFACE

Available in electronic format only

ANNEX 2:

TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

ANNEX 2:

TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table 1 Planned and on-going studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
MO28048 (SafeHER): A Phase III prospective, two cohort non-randomized, multicentre, multinational, open label study to assess the safey of assisted- and self-administered subcutaneous Herceptin as adjuvant therapy in patients with operable HER2-positive early breast cancer. **Category 3**	*Primary Objective* To assess the overall safety and tolerability of subcutaneous (SC) Herceptin in HER2-positive early breast cancer (EBC) patients with assisted administration using a conventional syringe and needle (vial formulation) and with assisted administration with or without self-administration using a single-use injection device (SID). *Exploratory Objectives* To assess the immunogenicity of Herceptin and recombinant human hyaluronidase (rHuPH20) in a subset of patients receiving Herceptin SC using the SID (Cohort B) at select sites.	Immunogenicity/Hypersensitivity and anaphylaxis of Herceptin SC Short term safety of Herceptin SC compared to Herceptin IV	Interim Analyses: Annual reports submitted with PBRER/PSUR Final Report: 2020
BO29159 (MetaPHER) A multicenter, open-label, single-arm study of Herceptin SC in combination with Perjeta and Docetaxel	*Primary objective:* To evaluate the safety and tolerability of Herceptin subcutaneous (SC) in combination with Perjeta plus docetaxel in patients with human epidermal growth factor receptor 2 (HER2)-positive advanced	Immunogenicity/Hypersensitivity and Anaphylaxis Herceptin SC Cardiac dysfunction	Interim CSR submitted December 2017, in support of a Type II variation application for Perjeta (EMEA/H/C/2547/II /0035) to update the Perjeta SmPC to allow administration of Perjeta with

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
in first-line treatment of patients with HER2-positive advanced breast cancer (metastatic or locally recurrent) **Category 3**	(metastatic or locally recurrent) breast cancer. *Secondary Objectives* The secondary objectives for this study are to evaluate Herceptin SC in combination with Perjeta intravenous (IV) plus docetaxel with respect to: Efficacy parameters (see protocol) Progression-free survival (PFS) Overall Survival (OS) Objective response rate (ORR) • Incidence of anti-Herceptin and anti-rHuPH20 antibody formation		Herceptin SC. Positive Commission Decision issued on 30 April 2018. Final Report:2019: The final CSR (September 2019) to be submitted to EMA in November 2019 via a Type II variation (EMEA/H/C/278/II/XX)

ADS= annual data summary; EBC=early breast cancer; FDA= Food and Drug Administration; HER2= human epidermal growth factor receptor 2; IUGR= intrauterine growth restriction; IV= intravenous; ORR= objective response rate; OS= overall survival; PBRER= Periodic Benefit-Risk Evaluation Report; PFS=progression-free survival; PSUR= Periodic Safety Update Report; rHuPH20= recombinant human hyaluronidase; SC=subcutaneous; SGA=small for gestational age; SID= single-use injection device

Note: The MetaPHER final CSR will be submitted to the EMA together with EU RMP version 21.0. This study is retained as ongoing in the present EU RMP update. The study will be moved to completed studies after CHMP approval in subsequent RMP updates.

Table 2 Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
H4613g (HER-Q-Les) A Phase 1b, single-arm, open label clinical trial to evaluate corrected QT interval and drug drug interaction of traztuzumab on carboplatin in the presence of docetaxel in patients with metastatic or locally advanced inoperable cancer **Category 3**	1) To conduct a QT interval protocol according to the principles of ICH E14 (The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs), Section IID, in a minimum of 50 patients receiving Herceptin (ICH E14 2005). 2) To perform a drug–drug interaction (DDI) trial in patients with metastatic or locally advanced inoperable cancer who are positive for human epidermal growth factor receptor 2 (HER2).	Cardiac dysfunction	Final Clinical Study Report (CSR) (for Electrocardiogram, Safety, and Exploratory Efficacy Analyses Only): RESEARCH REPORT NO. 1055676 September 2013. Final (CSR) (for DDI analyses only): RESEARCH REPORT NO. 1052626 January 2013. The Final CSR was assessed under variation EMEA/H/C/000278/II/89G, approved on 22 February 2016.
BO27798 (HELOISE): A randomized, open-label, multicenter Phase IIIb study comparing two trastuzumab dosing regimens, each in combination with cisplatin/capecitabine	Primary Objective To compare the duration of OS in patients who are randomized at enrollment to treatment with one of two Herceptin dosing regimens (loading dose of 8 mg/kg followed by either 6 mg/kg or 10 mg/kg maintenance doses given every 3 weeks), plus cisplatin and capecitabine. Secondary Objectives To compare the duration of OS in patients	Safety and tolerability of the two Herceptin treatment regimens (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks or 8 mg/kg loading dose followed by 10 mg/kg every 3 weeks).	Interim Analysis First PK: 31 May 2013. 2nd PK: 9 March 2015 Final CSR April 2016 Final CSR submitted to EMA in April 2016 and assessed under Type II variation EMEA/H/C/000278/II/112, approved (positive Committee for

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
chemotherapy, as first-line therapy in patients with HER2-positive metastatic gastric or gastro-esophageal junction adenocarcinoma who have not received prior treatment for metastatic disease. **Category 3**	on the two Herceptin treatment arms who are found to have Herceptin Cmin values <12 µg/mL on Cycle 1 Day 21. To assess Herceptin concentrations during treatment Cycle 1 and Herceptin Cmin (Cycle 1 Day 21) values in additional treatment cycles through Cycle 11 (i.e., pre dose concentration before Cycle 12 = Cycle 11 Day 21 concentration) or until disease progression (whatever occurs first) for the two dosing regimens. To evaluate the safety and tolerability of Herceptin for the two dosing regimens. To compare the duration of progression free survival (PFS) and the overall objective response rate (ORR) in patients on the two Herceptin treatment arms who are found to have Herceptin Cmin values < 12 µg/mL on treatment Cycle 1 Day 21.		Medicinal Products for Human Use [CHMP] Opinion) on 15 September 2016.
BCIRG 006 /H2296s/GO00773 To evaluate genetic and biochemical markers for predicting risk of developing cardiac dysfunction and later cardiac events in these patient groups. **Category 3**	To evaluate genetic and biochemical markers for predicting risk of developing cardiac dysfunction and later cardiac events in these patient groups	Cardiac Dysfunction	Cardiac Marker sub-study completed: Research Report 1056458 June 2013. Submitted to EMA in June 2013 and assessed under Follow up Measure (FUM) 085 Final (CSR) December 2015, submitted to EMA in December 2015 and assessed under Type II variation

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
			EMEA/H/C/000278/II/104, approved (positive CHMP Opinion) on 18 February 2016.
MO22982 (PrefHer): A randomized, multi-center cross-over study to evaluate patient preference and HCP satisfaction with subcutaneous (SC) administration of trastuzumab in HER2-positive early breast cancer (EBC) **Category 3**	Primary To evaluate the proportion of patients indicating an overall preference for either the subcutaneous (SC) or the intravenous (IV) route of administration. Secondary To evaluate: The HCP satisfaction with SC Herceptin HCP perceived time savings with SC Herceptin Safety and tolerability Efficacy – event-free survival (EFS) Immunogenicity of Herceptin and recombinant human hyaluronidase (rHuPH20) in Cohort 1 (SID) only Exploratory Factors that influence patient preference for SC Herceptin Patient satisfaction with the single use injection device (SID)	Short-term safety of Herceptin SC compared to Herceptin IV.	Primary CSR (crossover period) completed and submitted Q3 2014. Final CSR December 2016, submitted to EMA in December 2016 and assessed under Type II variation EMEA/H/C/000278/II/126, approved (positive CHMP Opinion) on 23 February 2017.
ML20529 Prospective, randomized, pharmacological	Primary Objective: To determine whether concurrent ATII-antagonist treatment can prevent Herceptin-related cardiotoxicity, defined as	Cardiac dysfunction	Final report: Investigator final publication provided, submitted with 2016 PBRER (November 2016).

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
intervention study evaluating the effect of the angiotensin II-receptor (AT1) blocker candesartan versus placebo in prevention of trastuzumab-associated cardiotoxicity in patients with primary breast cancer treated with trastuzumab. **Category 3**	a decline in LVEF of more than 15% or a decrease of less than 15% to an absolute value below 45%. Secondary objectives: • To determine if 'Brain Natriuretic Peptide' (NT-proBNP) and troponin T can be used as surrogate marker in the monitoring of trastuzumab-associated cardiotoxicity • To determine genetic variability in relevant genes such as the HER2 gene (by assessing single nucleotide polymorphisms [SNPs] in the kinase domain) and explore any correlations with trastuzumab induced cardiotoxicity • To determine the reversibility of a decrease in left ventricular ejection fraction (LVEF) associated with trastuzumab treatment		
BO20652 (OHERA) An observational study of cardiac events in Patients with HER2 positive early breast cancer treated with Herceptin.	Primary objective: To observe the incidence of symptomatic congestive heart failure (CHF) (NYHA class II, III and IV) and cardiac death in patients treated with Herceptin in routine clinical practice setting. Secondary objectives: To explore potential risk factors for	Cardiac dysfunction	Interim Analyses: Annual Safety Report (ASR), submitted with September PBRER/PSUR. Last ASR submitted with September 2015 PBRER/PSUR. ASR scheduled for 2016 deferred to

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
Category 3	symptomatic congestive heart failure. To observe the time to onset and the time to recovery of symptomatic congestive heart failure. To observe the incidence of asymptomatic cardiac failure and other significant cardiac conditions.		the final analysis (CSR) in July 2017 Final report: By end July 2017. Final CSR submitted in June 2017 and assessed under Type II variation EMEA/H/C/000278/II/135, approved (positive CHMP Opinion) on 28 September 2017.
BO22227 (HannaH) A phase III, randomized, open-label study to compare pharmacokinetics, efficacy and safety of subcutaneous (SC) Herceptin with intravenous (IV) Herceptin administered in women with HER2 positive early breast cancer (EBC). **Category 3**	<u>Primary Objectives:</u> To compare between SC Herceptin and IV Herceptin in the neoadjuvant setting • the serum trough concentrations (Ctrough) observed pre-surgery • the efficacy (pathological complete response, pCR) <u>Secondary objectives:</u> • To compare between SC Herceptin and IV trastuzumab; the observed C_{trough} concentrations post-surgery the predicted C_{trough} concentrations pre-surgery and post-surgery the pharmacokinetic profile. To evaluate in the SC Herceptin and IV Herceptin arm; total pathological complete response (tpCR) overall response rate (ORR) time to response (TTR) event-free survival (EFS) OS safety and tolerability immunogenicity.	Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin	Interim Analyses: Annual summary submitted with March PBRER/PSUR in 2015; Final (CSR): 1079038. September 2017 Final (CSR) submitted to EMA on 12 December 2017 and assessed under Type II variation EMEA/H/C/000278/II/140, approved (positive CHMP Opinion) on 22 March 2018.

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
H4621g/GE28099 (MotHER An observational study of pregnancy and pregnancy outcomes in women with breast cancer treated with Herceptin, Perjeta in combination with Herceptin, or Kadcyla during pregnancy or within 7 months prior to conception. **Category 3**	With the approval of Herceptin for the treatment of HER2-positive breast cancer in the adjuvant and metastatic settings, of Perjeta plus Herceptin in the neoadjuvant and metastatic settings, and of Kadcyla in the metastatic setting, there is a potential for women of childbearing age to become pregnant while receiving any of these therapies for the treatment of breast cancer. *Primary objective:* To describe adverse pregnancy complications such as oligohydramnios; pregnancy outcomes such as live births, fetal deaths/stillbirths (at > 20 weeks of gestation), and abortions; fetal/infant outcomes such as major malformations, deformations, and disruptions; and fetal or infant functional deficits among women (and their offsprings) with breast cancer following treatment with Herceptin, Perjeta, or Kadcyla during pregnancy or within 7 months prior to conception. *Secondary objective:* To describe the following: spontaneous, therapeutic, or elective abortions (at ≤ 20 weeks of gestation); premature births (at < 37 weeks of gestation); being small for gestational age (SGA) (i.e., birth weight below the 10th percentile); intrauterine growth restriction (IUGR); and other	Oligohydramnios	Interim Analysis: Annual report submitted with Periodic Benefit-Risk Evaluation Report/ Periodic Safety Update Report (PBRER/PSUR). Final Report: The U.S. Food and Drug Administration (FDA) asked the Sponsor to submit a final report for Herceptin only in 2018 for early fulfilment of its post-marketing commitment (BL 103792/S-5175 PMC#3). The MotHER Annual Data Summary (ADS) for 2018 presented data for all patients enrolled in the Registry. This ADS was the final report for patients exposed to Herceptin only and was submitted to U.S. FDA in April 2018. The MotHER Registry is closed The ADS for 2018 covering the cumulative time period from 20 December 2008 (when the Registry was initiated) through 31 January 2018, and includes reporting interval (1 February 2017 through 31 January 2018) as well as the ADS for 2017 covering the cumulative time period from 20 December 2008 through 31 January 2017 and includes the prior reporting interval 1 February

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
	complications specific to pregnancy and delivery.		2016 through 31 January 2017 was submitted to European Medicines Agency (EMA) in August 2018. These two reports werel also presented in the 2-year Herceptin PBRER (data lock point: 24 September 2018) in December 2018.

ASR= annual safety report; AT1= angiotensin II-receptor;CHF=congestive heart failure; CHMP= Committee for Medicinal Products for Human Use; CSR= Clinical Study Report; DDI=drug-drug interaction; EBC=early breast cancer; EFS=event-free survival; EMA=European Medicines Agency; HCP=healthcare professional; HER2= human epidermal growth factor receptor 2; ICH=International Conference on Harmonization; IV=intravenous; LVEF= left ventricular ejection fraction; NYHA=New York Heart Association; ORR= objective response rate; OS= overall survival; PBRER= Periodic Benefit-Risk Evaluation Report; pCR= pathological complete response; PFS=progression-free survival; PSUR= Periodic Safety Update Report; rHuPH20= recombinant human hyaluronidase; SC=subcutaneous; SID= single-use injection device; SNP= single nucleotide polymorphisms; tpCR= total pathological complete response; TTR= time to response.

ANNEX 3:

PROTOCOLS FOR PROPOSED, ONGOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

PROTOCOLS FOR PROPOSED, ONGOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

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1. PART A: REQUESTED PROTOCOLS OF STUDIES IN THE PHARMACOVIGILANCE PLAN, SUBMITTED FOR REGULATORY REVIEW WITH THIS UPDATED VERSION OF THE RMP

Not applicable.

2. PART B: REQUESTED AMENDMENTS OF PREVIOUSLY APPROVED PROTOCOLS OF STUDIES IN THE PHARMACOVIGILANCE PLAN, SUBMITTED FOR REGULATORY REVIEW WITH THIS UPDATED VERSION OF THE RMP

Not applicable.

3. PART C: PREVIOUSLY AGREED PROTOCOLS FOR ON-GOING STUDIES AND FINAL PROTOCOLS NOT REVIEWED BY THE COMPETENT AUTHORITY

Approved protocols:

- BO29159 (MetaPHER)[1]

Procedure number where the protocol was approved: EMEA/H/C/000278/MEA/095-095.1

Full protocols or links/references to eCTD documents: Submitted under MEA095 on 13 November 2013 under eCTD 0138

- MO28048 (SafeHER):

Procedure number where the protocol was approved: EMEA/H/C/000278/II/93

Full protocols or links/references to eCTD documents: This protocol was submitted under eCTD sequence 0216 with RMP version 16.3.

Since that time, the protocol has been updated to protocol version 4, (11 November 2016) and this is provided for information and completeness with the present submission eCTD sequence (eCTD sequence 0295).

Enhanced pregnancy PV Program:

Procedure number where the protocol was approved: EMEA/H/C/000278/II/93

[1] The MetaPHER final CSR will be submitted to the EMA in November 2019 together with EU RMP version 21.0. This study is retained as ongoing in the present EU RMP update. The study will be moved to completed studies after CHMP approval in subsequent RMP updates

Full protocols or links/references to eCTD documents: This protocol was submitted under eCTD sequence 0216 with RMP version 16.3.

Final Protocols Not Reviewed or Not Approved:

Not applicable

PROTOCOL

TITLE:	**A MULTICENTER, OPEN-LABEL, SINGLE-ARM SAFETY STUDY OF HERCEPTIN® SC IN COMBINATION WITH PERJETA® AND DOCETAXEL IN TREATMENT OF PATIENTS WITH HER2–POSITIVE ADVANCED BREAST CANCER (METASTATIC OR LOCALLY RECURRENT)**
PROTOCOL NUMBER:	BO29159
VERSION NUMBER:	2
EUDRACT NUMBER:	2014-001458-40
TEST PRODUCTS:	Herceptin® for subcutaneous administration (RO0452317) Perjeta® (RO4368451)
MEDICAL MONITORS:	[redacted], Pharm.D. [redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	20 October 2014
DATE AMENDED:	Version 2: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	12-Mar-2015 04:48:36

PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

Protocol BO29159 has been amended to correct a typographical error in one of exclusion criteria from “at least” to “less than.”

No additional changes have been made. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 2:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 4.1.2: Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry. Assessments must be performed according to the timing specified in the Schedule of Assessments (see Appendix 1):

2. Disease-free interval of ~~at least~~ *less than* 6 months from completion of adjuvant or neoadjuvant systemic non-hormonal treatment to recurrence of breast cancer

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LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTICENTER, OPEN-LABEL, SINGLE-ARM SAFETY STUDY OF HERCEPTIN® SC IN COMBINATION WITH PERJETA® AND DOCETAXEL IN TREATMENT OF PATIENTS WITH HER2–POSITIVE ADVANCED BREAST CANCER (METASTATIC OR LOCALLY RECURRENT)**
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MEDICAL MONITORS:	[redacted], Pharm.D. [redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature Date

Please return the signed original copy of the form as instructed by your local study monitor. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, OPEN-LABEL, SINGLE-ARM SAFETY STUDY OF HERCEPTIN® SC IN COMBINATION WITH PERJETA® AND DOCETAXEL IN TREATMENT OF PATIENTS WITH HER2–POSITIVE ADVANCED BREAST CANCER (METASTATIC OR LOCALLY RECURRENT)**
PROTOCOL NUMBER:	BO29159
VERSION NUMBER:	2
EUDRACT NUMBER:	2014-001458-40
TEST PRODUCT:	Herceptin® for subcutaneous administration (RO0452317) Perjeta® (RO4368451)
PHASE:	IIIb
INDICATION:	Advanced breast cancer (metastatic or locally recurrent)
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Primary Objectives

Primary Safety Objective

The primary objective for this study is to evaluate the safety and tolerability of Herceptin subcutaneous (SC) in combination with Perjeta intravenous (IV) plus docetaxel in patients with human epidermal growth factor 2 (HER2)–positive advanced (metastatic or locally recurrent) breast cancer.

- Overall safety profile as determined by adverse events of any grade of severity, and adverse events Grade ≥ 3 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0) and cardiac function will be assessed including the following: cardiac events Grade ≥ 3, congestive heart failure (CHF), and cardiac death (see protocol)

Secondary Objectives

The secondary objectives for this study are to evaluate Herceptin SC in combination with Perjeta IV plus docetaxel with respect to:

- Efficacy parameters (see protocol)
  - Progression-free survival (PFS)
  - Overall Survival (OS)
  - Objective response rate (ORR)
- Incidence of anti-Herceptin and anti-rHuPH20 antibody formation

Study Design

Description of Study

This is an open-label, single-arm, multicenter, Phase IIIb study to evaluate the safety and tolerability of Herceptin SC in combination with Perjeta IV plus docetaxel (see figure below). Patients with HER2–positive advanced breast cancer (metastatic or locally recurrent) who have not previously received systemic non–hormonal anti-cancer therapy in the metastatic setting are

eligible to participate in the study. Enrollment is defined as first dose of study drug administration.

Four hundred patients are planned to be enrolled into the study at approximately 110 centers worldwide. Details of the study treatment are given in protocol.

Treatment Period

Every 3 weeks (21 days) the patient will receive Herceptin SC (fixed dose of 600 mg/5 mL), Perjeta IV (loading dose of 840 mg followed by 420 mg on Day 1 of each subsequent cycle), and docetaxel IV (at least six cycles with recommended initial dose of 75 mg/m^2). After Cycle 6, continuation of docetaxel treatment is at the discretion of the treating physician in agreement with the patient. The dose of docetaxel may be escalated to 100 mg/m^2 at the investigator's discretion on subsequent cycles if the initial dose is well tolerated.

End of Treatment

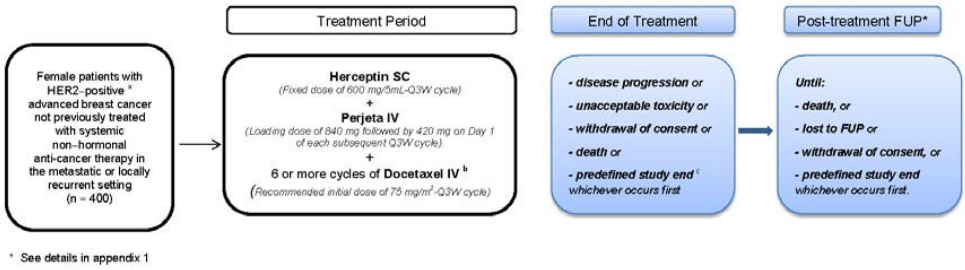
End of treatment for each patient is defined as receiving study medication until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end, whichever occurs first.

Post-Treatment Follow-up

If the patient discontinues all study treatments because of unacceptable toxicity, she will enter in follow-up and will have tumor assessments every 9 weeks (±3 days) until disease progression or predefined end of the study (see protocol), whichever occurs first.

In addition, patients with disease progression will continue to be followed until death, loss to follow-up, withdrawal of consent, predefined study end (see protocol), or study termination by Roche.

Figure: Study Design



FUP = follow-up; HER2 = human epidermal growth factor receptor 2; IV = intravenous; Q3W = every 3 weeks; SC = subcutaneous.

See protocol for dose administration guidelines.

[a] Defined as either immunohistochemistry 3 + or in situ hybridization positive.

[b] After Cycle 6, continuation of docetaxel treatment is at the discretion of the treating physician in agreement with the patient. The dose of docetaxel may be escalated to 100 mg/m^2 at the investigator's discretion on subsequent cycles if the initial dose is well tolerated.

[c] Cutoff of Final Safety Analysis will occur 24 months after the last patients is recruited (see protocol).

Number of Patients

The proposed sample size to be enrolled in this study is 400 patients with the following rationale:

- The width of the 95% Pearson Clopper CI of the incidence of Grade ≥3 adverse events is reasonably small (71.8%, 80.3%) with 400 treated patients based on the observed incidence of Grade ≥3 adverse events of 76.2% for patients who were treated with Perjeta in combination with Herceptin IV in the TOC4129g/WO20698 study.

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- Furthermore, with 400 treated patients on the observed incidence of cardiac events Grade ≥3 of 1.7% reported in the TOC4129g/WO20698 study, the width of the 95% Pearson Clopper CI of the incidence of Grade ≥3 cardiac adverse events is reasonably small (0.7%, 3.6%).

Target Population

Patients must meet the following criteria for study entry according to the timing specified in the Schedule of Assessments (see protocol):

1. Signed, written informed consent approved by the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC)
2. Female patients aged 18 years or older
3. Histologically or cytologically confirmed and documented adenocarcinoma of the breast with metastatic or locally recurrent disease not amenable to curative resection. Patients with measurable and/or non-measurable disease evaluable according to Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (see protocol) are eligible.

   Notes:

   - Patients with only bone metastases are eligible provided that they have some bone metastases that have not been previously irradiated and tumor tissue samples from the primary tumor are available for local HER2 testing.
   - Locally recurrent disease must not be amenable to resection with curative intent.
   - Patients with de novo Stage IV disease are eligible.
4. HER2-positive disease (defined as either immunohistochemistry [IHC] 3+ or in situ hybridization [ISH] positive) as assessed by local laboratory on primary tumor or metastatic site if primary tumor not available (positive ISH is defined as a ratio of ≥2.0 for the number of HER2 gene copies to the number of signals for CEP17, or for single probe tests, a HER2 gene count >4).
5. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 (see protocol)
6. Left ventricular ejection fraction (LVEF) of at least 50%
7. Negative serum pregnancy test result in women of childbearing potential (WOCBP; defined as premenopausal or <12 months of amenorrhea postmenopause and who have not undergone surgical sterilization)
8. WOCBP must agree to use a highly effective, non-hormonal form of contraception (such as surgical sterilization) or two effective forms of non-hormonal contraception or true abstinence during the treatment period and for at least 7 months after discontinuation of study treatment (see protocol for details).
9. Life expectancy of at least 12 weeks

Patients who meet any of the following criteria will be excluded from study entry. Assessments must be performed according to the timing specified in the Schedule of Assessments (see protocol):

1. Previous systemic non-hormonal anti-cancer therapy for the metastatic or locally recurrent disease. Note: Prior to study entry, up to two lines of hormonal therapy for metastatic or locally recurrent disease are permitted, one of which may be in combination with everolimus.
2. Disease-free interval of *less than* 6 months from completion of adjuvant or neoadjuvant systemic non-hormonal treatment to recurrence of breast cancer
3. Previous approved or investigative anti-HER2 agents as neoadjuvant or adjuvant therapy for any breast cancer treatment, except Herceptin
4. History of persistent Grade 2 or higher hematological toxicity resulting from previous adjuvant or neoadjuvant therapy

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5. Patients with radiographic evidence of CNS metastases as assessed by computed tomography or magnetic resonance imaging (MRI) that are not well controlled (i.e., are symptomatic or require control with continuous corticosteroid therapy [e.g., dexamethasone]). Note: Patients with CNS metastases are permitted to participate in the study if they have been stable in the 3 months prior to screening (as assessed by the investigator) after receiving local therapy (irradiation, surgery, etc.) but have not received anti-HER2 therapy.
6. Current peripheral neuropathy of Grade 3 or greater
7. History of other malignancy within the last 5 years prior to first dose of study drug administration (dosing), except for carcinoma in situ of the cervix or basal cell carcinoma
8. Inadequate organ function, evidenced by the following laboratory results:
    a) ANC < 1500 cells/mm^3
    b) Platelet count $< 100{,}000$ cells/mm^3
    c) Hemoglobin < 9 g/dL
    d) Total bilirubin greater than the upper limit of normal (ULN; unless the patient has documented Gilbert's syndrome)
    e) AST (SGOT) or ALT (SGPT) $> 2.5 \times$ ULN
    f) AST (SGOT) or ALT (SGPT) $> 1.5 \times$ ULN with concurrent serum alkaline phosphatase $> 2.5 \times$ ULN. Serum alkaline phosphatase may be $> 2.5 \times$ ULN only if bone metastases are present and AST (SGOT) and ALT (SGPT) are $< 1.5 \times$ ULN
    g) Serum creatinine > 2.0 mg/dL or 177 µmol/L
    h) INR and aPTT or PTT $> 1.5 \times$ ULN (unless on therapeutic anticoagulation)
9. Uncontrolled hypertension (systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg) with or without medication
10. Clinically significant cardiovascular disease as follows:
    a) Cerebrovascular accident/stroke or myocardial infarction within 6 months prior to first study medication, or
    b) Unstable angina, or
    c) History of or active CHF of any NYHA criteria, or
    d) History of or ongoing serious cardiac arrhythmia requiring medication (except controlled atrial fibrillation or paroxysmal supraventricular tachycardia)
11. History of LVEF decline to below 50% during or after prior Herceptin neoadjuvant or adjuvant therapy
12. Current known infection with HIV, hepatitis B virus, or hepatitis C virus
13. Severe uncontrolled concomitant disease that would contraindicate the use of any of the investigational drugs used in this study or that would put the patient at high risk for treatment-related complications: such as uncontrolled systemic disease (e.g., pulmonary [including interstitial lung disease]) or metabolic disease, wound healing disorders, ulcers, or bone fractures
14. Pregnant or lactating women
15. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy
16. Major surgical procedure or significant traumatic injury within 14 days prior to first dose of study drug administration (dosing) or anticipation of need for major surgery during the course of study treatment. Note: Should surgery be necessary during the course of the study, patients should be allowed to recover for a minimum of 14 days prior to subsequent study treatment.
17. Receipt of IV antibiotics for infection within 14 days prior to first dose of study drug administration

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18. Current chronic daily treatment (continuous for >3 months) with corticosteroids (dose ≥ 10 mg/day methylprednisolone), excluding inhaled steroids
19. Known hypersensitivity to any of the study medications or to excipients of recombinant human or humanized antibodies
20. History of receiving any investigational treatment within 28 days prior to first dose of study drug administration (dosing)
21. Assessed by the investigator as unable or unwilling to comply with the requirements of the protocol
22. Concurrent participation in any interventional clinical trial

Length of Study

The study duration will be approximately 42 months, including 18 months of recruitment and 24 months of treatment/follow-up after the last patient has been enrolled.

End of Study

The primary objective of this study is the safety outcome. The study will end at the time of the cutoff for the final analysis, **24 months** after the last patient has been enrolled, or all patients in the study have withdrawn consent, died, or if the study is prematurely terminated by the Sponsor, whichever occurs first.

All patients who are still receiving study treatment at time of cutoff for the final analysis will have their post-treatment safety follow-up visit 28–35 days after the last dose of study treatment, and then will be considered as finished with their participation in the study; these patients will continue to be followed in accordance with the local standard of care.

These patients may be provided with commercial drug for continuation of treatment. This will depend on the local availability of commercial Herceptin SC, Herceptin IV, and Perjeta.

The post-study adverse events (see protocol) should be reported directly to Roche Safety Risk Management and not on the eCRF. This data collection will be restricted to reporting of serious adverse events that are believed to be related to study drug treatment.

Outcome Measures

Efficacy Outcome Measures

Efficacy outcome measures (secondary objectives) for this study are to evaluate Herceptin SC in combination with Perjeta IV plus docetaxel with respect to:

- PFS based on investigator assessment is defined as the time from first dose of study drug administration to the first radiographically documented progression of disease, as determined by the investigator using current RECIST v1.1 (see protocol) or death from any cause, whichever occurs first. Carcinomatous meningitis diagnosed by cytologic evaluation of cerebral spinal fluid will also define progressive disease (PD). Medical photography will also be allowed to monitor chest wall recurrences of subcutaneous lesions.
- OS is defined as the time from the date of first dose of study drug administration to the date of death from any cause.
- ORR is defined as a complete response (CR) or partial response (PR) determined by the investigator using RECIST v1.1 (see protocol) on two consecutive occasions ≥ 4 weeks apart. Patients with disease localized only to the bone will not be included in the analysis of objective response.

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events Grade ≥ 3
- Incidence and severity of all serious adverse events
- Incidence and severity of all adverse events
- Incidence of congestive heart failure (CHF) and cardiac death

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- LVEF over the course of the study and decline in LVEF from baseline
- Cause of death while in the study
- Incidence of adverse events leading to discontinuation
- Incidence of adverse events leading to dose modification
- Clinically relevant laboratory test abnormalities (see protocol for details)
- Incidence of anti-Herceptin and anti-rHuPH20 antibodies

Investigational Medicinal Products

Herceptin SC and Perjeta IV are considered to be the investigational medicinal products in this study.

Herceptin SC, Perjeta IV, and docetaxel should be administered sequentially as per table below: Herceptin SC will be administered first, followed by Perjeta IV and then docetaxel IV. An observation period of 30–60 minutes must be followed between each injection.

Herceptin SC

A fixed dose of 600 mg/5 mL Herceptin SC, irrespective of the patient's weight, will be administered throughout the treatment phase. All doses of Herceptin SC will be administered as an SC injection into the thigh by a trained health care professional over a period of 2–5 minutes. New injections should be given at least 2.5 cm from the old injection site(s) and never into areas where the skin is red, bruised, tender, or hard. During the course of treatment with Herceptin SC, other medicinal products for SC administration should preferably be injected at different sites.

Patients should be observed for 6 hours after the first injection (Cycle 1 Day 1) of Herceptin SC and for 2 hours after subsequent injections of Herceptin SC (from Cycle 2 onward) for signs or symptoms of administration-related reactions.

Perjeta IV

Perjeta will be administered as an IV infusion on Day 1 of the first treatment cycle as a loading dose of 840 mg, followed by 420 mg on Day 1 of each subsequent 3-week cycle. The medicinal products should be administered sequentially: Herceptin SC first, Perjeta IV, and then docetaxel IV, as per table below.

Initial infusions of Perjeta will be administered over 60 (±10) minutes and patients will be observed for an additional 60 minutes from the end of infusion for infusion-associated symptoms such as fever, chills, etc. Interruption or slowing of the infusion may reduce such symptoms. If the infusion is well tolerated, subsequent infusions may be administered over 30–60 (±10) minutes, with patients observed for an additional 30 minutes from the end of the infusion for infusion-associated symptoms.

Non-Investigational Medicinal Products

Docetaxel IV Chemotherapy

Docetaxel is considered to be a non-investigational medicinal product in this study.

Docetaxel will be administered in line with the respective product information and/or recognized clinical practice guidelines. It will be administered after Herceptin SC and Perjeta IV (see table below).

Summary of Study Treatment Dose and Schedule

Cycle	Herceptin SC	Perjeta IV	Docetaxel IV
Cycle 1	Day 1: A fixed dose of **600 mg/5 mL** Herceptin SC administered over 2–5 minutes	Day 1: Perjeta IV administration **60 minutes** after the end of he Herceptin SC administration **840 mg loading dose,** administered over 60 minutes	Day 1: Docetaxel IV administration **60 minutes** after the end of the Perjeta IV administration **75 mg/m^2** administered over 60 minutes Cycle 1
	Patients to be observed **for 6 hours after the first injection of Herceptin SC**	Followed by a 60-minute observation period after the first Perjeta IV administration	Observe according to institution standards for docetaxel IV administration
From Cycle 2	Day 1: A fixed dose of **600 mg/5 mL** Herceptin SC, administered over 2–5 minutes	Day 1: Perjeta IV administered **60 minutes** after the end of he Herceptin SC administration **420 mg dose** administered over 60 minutes (or 30–60 minutes if well tolerated)	Day 1: Docetaxel IV administered **30–60 minutes** after the end of the Perjeta IV administration **75 mg/m^2 (or 100 mg/m^2)**[b] administered over 60 minutes
	Patients to be observed for **2 hours after subsequent injections of Herceptin SC**	Followed by a 30 to 60-minute observation period after the subsequent Perjeta IV administration	Observe according to institution standards for docetaxel IV administration

IV = intravenous; SC = subcutaneous.

[a] One cycle every 3 weeks (21 days).

[b] Docetaxel IV for at least 6 cycles: After Cycle 6, continuation of docetaxel treatment is at the discretion of the treating physician and in agreement with the patient.

Statistical Methods

Final Safety Analysis

The safety analyses will include all enrolled patients who received at least one dose of any study drug.

The safety variables are all adverse events, adverse events Grade ≥ 3 according to the NCI CTCAE v4.0, adverse events leading to treatment interruption and discontinuation, serious adverse events, causes of deaths, incidence of CHF, incidence of cardiac adverse events Grade ≥ 3, LVEF decline (≥ 10% points from baseline to below 50%), premature discontinuation from study and treatment, and laboratory parameters. The primary interest in this study will be to estimate the incidence of adverse events Grade ≥ 3 for the treatment of Herceptin SC in combination with Perjeta and docetaxel.

The analysis of adverse events will focus on treatment-emergent adverse events (i.e., adverse events that occur during or after the first administration of study drug). Non–treatment-emergent adverse events (i.e., those that occur during screening) will be listed only during the screening period. Only the serious adverse event related to a protocol-mandated procedure will be reported and all adverse events that occurred before Day 1 (first administration) would be reported in medical history.

The incidence, type, and severity of adverse events will be summarized according to the primary System Organ Class (SOC) and within each SOC, by MedDRA preferred term.

Adverse events Grade ≥ 3, adverse events leading to treatment modification and discontinuation, and serious adverse events will be analyzed in a similar way to all adverse events. Causes of deaths will also be summarized and listed.

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LVEF as well as changes from baseline over time will be analyzed using descriptive statistics for continuous variable and presented graphically over time with associated 95% CI. The percentage of patients with an LVEF decline ≥ 10% points from baseline to below 50% will be summarized.

The number of patients who prematurely discontinue from study treatment with a corresponding reason for discontinuation will be summarized and listed. The discontinuation from study will be also summarized and listed.

Descriptive statistics will be presented for cumulative study medication doses and duration of exposure.

Subgroup analysis of all grade adverse event variables will be performed for patients receiving at least one cycle of 100 mg/m^2 docetaxel.

The following subgroup analysis will be performed for LVEF decline of more than 10% points from baseline to below 50%, CHF, cardiac adverse events Grade ≥ 3:

- Other selected safety variables—race
- Known risk factors for development of cardiac related events—age, medical history of hypertension, prior treatment with anthracyclines, LVEF at baseline

The incidence and severity of administration-related reaction (ARR) adverse events will be summarized. Time to onset of the first ARRs and time from onset to resolution of ARRs will also be summarized. In addition, the ARR analyses will also be performed for each treatment cycle.

Laboratory parameters, hematology, and serum biochemistry will be presented in shift tables of NCI CTCAE v4.0 grade at baseline versus worst grade during the treatment period. The summary of laboratory parameters will also be presented by means, standard deviation, minimum, and maximum. The selected laboratory parameters will be also graphically presented over time.

Determination of Sample Size

The main objective of this safety study is the characterization of the safety profile and tolerability of Herceptin SC in combination with Perjeta IV and docetaxel based on an estimation of the incidence of adverse events. This is not a hypothesis testing study but an exploratory study with predefined precision of estimates for key safety parameters for sample size determination; there are no formal statistical hypothesis tests to be performed, and there will be no adjustments for multiplicity of endpoints or within-subgroups comparisons.

The proposed sample size to be enrolled in this study is 400 patients with the following rationale:

- The width of the 95% Pearson Clopper CI of the incidence of Grade ≥ 3 adverse events is reasonably small (71.8%, 80.3%) with 400 treated patients based on the observed incidence of Grade ≥ 3 adverse events of 76.2% for patients who were treated with Perjeta in combination with Herceptin IV in the TOC4129g/WO20698 study.
- Furthermore, with 400 treated patients on the observed incidence of cardiac events Grade ≥ 3 of 1.7% reported in the TOC4129g/WO20698 study, the width of the 95% Pearson Clopper CI of the incidence of Grade ≥ 3 cardiac adverse events is reasonably small (0.7%, 3.6%).

Interim Analyses

In addition to the final analysis, there will be an interim analysis approximately 6 months after recruitment of the last patient to determine overall safety and tolerability with special emphasis on cardiac safety and efficacy. Given the objective of the study, the Sponsor may choose to adapt the timepoint of the interim analysis or to conduct additional interim analyses if appropriate. The decision to adapt the timepoint of the interim analysis or to conduct an additional interim analysis will be documented in the Sponsor's trial master file prior to the conduct of the respective interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

There will also be an annual review of safety data by the IMC.

Herceptin® SC and Perjeta®—F. Hoffmann-La Roche Ltd
18/Protocol BO29159, Version 2

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
ARR	administration-related reaction
AUC	area under the concentration curve
CHF	congestive heart failure
CR	complete response
CRO	clinical research organization
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	serum trough concentration
CVAD	central venous access device
EBC	early breast cancer
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EGFR	epidermal growth factor receptor
EPP	efficacy per protocol (population)
ER	estrogen receptor
ESMO	European Society of Medical Oncology
FDA	U.S. Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
HER	human epidermal growth factor
HER2	human epidermal growth factor 2
Herceptin IV	Herceptin for intravenous administration
Herceptin SC	Herceptin for subcutaneous administration
HR	hazard ratio
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMC	Internal Monitoring Committee
IMP	investigational medicinal product

Abbreviation	Definition
IND	Investigational New Drug
IRB	Institutional Review Board
IRF	Independent Review Facility
ISH	in situ hybridization
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IxRS	interactive voice/Web response system
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition (scan)
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
pCR	pathologic complete response
PD	progressive disease
PFS	progression-free survival
PI3-K	phosphatidylinositol 3-kinase
PR	partial response
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
rHuPH20	recombinant human hyaluronidase
SC	subcutaneous
SD	stable disease
SID	single-use injection device
SOC	System Organ Class
TK	tyrosine kinase
ULN	upper limit of normal
WOCBP	women of childbearing potential

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

Breast cancer is the most common cancer in women with a global prevalence of more than 1 million patients and approximately 450,000 deaths annually (Ferlay et al. 2010). While improved early detection and advances in systemic therapy for early-stage disease have resulted in a small decline in breast cancer mortality since 1989, metastatic breast cancer (MBC) remains largely incurable with a median survival of approximately 24 months (National Cancer Institute [NCI] 2011). Factors associated with poor survival include age ≥50 years, visceral disease, shorter disease-free intervals, aneuploid tumors, tumors with a high S-phase fraction, p53 accumulation, low bcl-2 expression, negative hormone receptor status, and positive human epidermal growth factor 2 (HER2) status (Chang et al. 2003).

Although the treatment of MBC is palliative rather than curative in intent, improvement in length of survival is an important treatment goal. There is a significant need for new agents with novel mechanisms of action and non-overlapping toxicity that can be combined with established treatments for breast cancer.

1.2 BACKGROUND ON STUDY TREATMENTS

1.2.1 Human Epidermal Growth Factor Receptors

Evidence suggests that dysregulation of ligands and receptors of the human epidermal growth factor (HER) receptor family are important in the pathogenesis of cancer. The HER tyrosine kinase (TK) receptor family comprises four receptors: HER1 (epidermal growth factor receptor [EGFR]), HER2, HER3, and HER4. These receptors mediate tumor cell growth, survival, and differentiation (Sundaresan et al. 1999; Yarden and Sliwkowski 2001). HER receptors normally exist as inactive monomers.

Activation of HER receptors occurs following ligand binding, leading to receptor dimerization and cell signaling through the phosphatidylinositol 3-kinase (PI3-K)/AKT pathway for promotion of tumor cell survival and through the mitogen–activated protein kinase pathway for cellular proliferation.

HER2 has no known ligand and, in a state of overexpression, can form active homodimers and initiate TK signaling without ligand stimulation. Additionally, as HER2 concentrations increase, the incidence of HER2 interactions with other receptors also increases, resulting in a broad recruitment of a number of proteins (Jones et al. 2006). Recent data obtained using micro-array technology suggest that the HER2 receptor can bind to more than 17 different proteins and may recruit proteins that other HER receptors cannot recruit. These activities highlight the promiscuity of HER2 in its ability to bind to other HER receptors and initiate TK signaling through several mechanisms (Jones et al. 2006).

In approximately 15%–20% of patients, overexpression of HER2 is observed in primary breast cancers. Overexpression of HER2 in breast cancer has been correlated with high histologic grade, increased mitotic activity, p53 mutation, negative estrogen receptor (ER) status, absence of bcl-2, and absence of lobular architecture. In addition to associations with other known negative prognostic factors, HER2 overexpression has been independently associated with worse disease-free survival and overall survival (OS) compared with tumors that do not overexpress HER2 (Pauletti et al. 2000). Approximately 65% of breast cancers are ER–positive and progesterone receptor–positive (American Cancer Society 2011).

1.2.1.1 Herceptin® (Trastuzumab) for Subcutaneous Administration

Herceptin® (trastuzumab) is a humanized monoclonal antibody directed at the HER2 receptor. Herceptin IV is indicated for the treatment of patients with HER2–positive breast cancer both in the adjuvant and metastatic settings. The addition of Herceptin IV to standard chemotherapy increases time to progressive disease (PD) or the length of progression-free survival (PFS) and improves survival when given with chemotherapy to women with HER2–positive breast cancer (Slamon et al. 2001; Romond et al. 2005).

Clinical benefits are greatest in patients with tumors that strongly overexpress HER2, graded 3+ by immunohistochemistry (IHC) and/or tumors that have HER2 gene amplification (see the Herceptin Investigator's Brochure for details on nonclinical and clinical studies).

Herceptin for subcutaneous (SC) administration (Herceptin SC) has been developed by the Sponsor to address the known limitations of intravenous (IV) administration (e.g., long administration times, treatment barriers for patients with poor venous access, continued use of port-a-cath systems). The key excipient in the SC formulation of Herceptin is the enzyme recombinant human hyaluronidase (rHuPH20), which enables larger volumes to be administered without reduced tolerability and with improved patient acceptability. Hyaluronidase acts primarily as a permeation enhancer to increase the dispersion and absorption of other co-administered drugs. SC injection of Herceptin takes significantly less time (2–5 minutes) compared with an IV infusion (Herceptin IV; 30–90 minutes) and is expected to improve treatment convenience and patient compliance. Convenience and compliance are particularly important for patients treated over prolonged periods of time, such as in the adjuvant setting.

Herceptin SC is marketed across Europe and in other areas of the world as treatment for patients with HER2-positive early breast cancer (EBC) and MBC.

1.2.1.2 Recombinant Human Hyaluronidase (rHuPH20)

The feasibility and patient acceptability of SC administration of any drug is dependent on the volume of drug that must be administered. The key excipient in the SC formulation of Herceptin is the enzyme rHuPH20, recombinant human hyaluronidase, which enables larger volumes to be administered without reduced tolerability and with improved patient

acceptability. Hyaluronidase acts primarily as a permeation enhancer to increase the dispersion and absorption of other co-administered drugs. Hyaluronidase transiently hydrolyses hyaluronan, a component of the SC matrix, leading to reduced viscosity of the extracellular matrix of the hypodermis and, thus, to an improved delivery of subcutaneously administered drugs to the systemic circulation.

rHuPH20 has been developed to improve dispersion and absorption of co-administered drugs. This recombinant human molecule has a higher purity and is associated with improved tolerability compared with the animal-derived enzyme. The rHuPH20 (Hylenex® Prescribing Information 2013) is licensed in the United States to facilitate the absorption and dispersion of drugs when given subcutaneously at doses between 50 IU and 300 IU (Frost 2007). The rHuPH20 used in the current study is produced from a second generation of the Hylenex process that has improved yield and purity. This formulation has been combined with Herceptin to allow safe and comfortable SC injection of volumes of 2–5 mL.

1.2.1.3 Clinical Studies with Herceptin for Subcutaneous Administration

Herceptin SC (formulated with rHuPH20) Vial has been studied in two clinical trials (Studies BP22023 [CP2] and BO22227 [HannaH]) that used conventional handheld syringes and hypodermic needles to administer the study drug.

A study to assess the safety of assisted- and self-administered Herceptin SC Vial and Herceptin SC single-use injection device (SID) as therapy in patients with operable HER2–positive EBC (Study MO28048 [SafeHER]) is ongoing.

The primary objective of the Phase Ib dose–finding study (BP22023 [CP2]) was to select the dose of Herceptin SC that results in exposure comparable to that achieved with an IV dose of Herceptin.

The pharmacokinetic modeling of fixed Herceptin SC dose selection indicated that a flat and a weight-based dosing strategy would result in a comparable range of exposure with a relationship to body weight that is inverse, and a fixed dose of 600 mg/5 mL would result in serum trough concentration (C_{trough}) values that are at least as high as with the every 3 weeks (Q3W) IV regimen (8-mg/kg loading dose followed by 6-mg/kg maintenance dose).

The Phase III Study BO22227 demonstrated the non-inferiority of the C_{trough} and pathologic complete response (pCR) for Herceptin SC versus Herceptin IV (Ismael et al. 2012).

The overall safety profile of trastuzumab SC (including cardiac safety) was in line with the known safety profile of the trastuzumab IV formulation. A slightly higher difference between the treatment arms were observed in the incidences of serious adverse events,

serious adverse events of infection, adverse events leading to death, cardiac serious adverse events, and adverse events leading to treatment withdrawal, which were often based on rare events. There was no pattern of events observed in the serious adverse event reports. Exploratory analyses did not indicate an association between toxicity and exposure. Although the incidence of serious adverse events was higher for trastuzumab SC, the incidence of Grade ≥ 3 adverse events was similar in both treatment arms. Herceptin SC injections were generally well tolerated. As expected, Herceptin-related injection-site reactions were observed at a higher rate in the Herceptin SC arm (11.1% vs. 0.3% in the SC and IV arms, respectively). With the exception of five Grade 2 adverse events, all injection-site reactions were of Grade 1 intensity. Administration-related reactions (ARRs) were more common in the Herceptin SC arm (47.8% vs. 37.2% Herceptin SC and IV arms, respectively). Erythema and cough were the primary adverse events that caused the difference observed between treatment arms. In both study arms, most adverse events (>97%) were of Grade 1 or 2 intensity. The incidence of Grade ≥3 events was comparable across arms (54% in the Herceptin SC arm vs. 52% in the Herceptin IV arm). Fourteen percent of patients in the Herceptin IV arm experienced an adverse event that met “serious” criteria (i.e., a serious adverse event) compared with 22% of patients in the Herceptin SC arm. More patients in the Herceptin SC arms had infection events reported as serious. No pattern in types of events, affected System Organ Classes (SOCs), or latency accounted for the difference in rates. No relationship between the difference in serious adverse events and Herceptin exposure (area under the curve) or body weight was found.

A higher rate of anti-drug antibodies against Herceptin was observed for the Herceptin SC formulation compared with Herceptin IV (14.6% of patients [43/295] in the Herceptin SC arm vs. 7.1% of patients [21/296] in the Herceptin IV arm). One patient treated with the IV formulation and two patients treated with the SC formulation developed neutralizing anti-Herceptin antibodies. The higher incidence of antibody development in the SC arm was not associated with adverse events or altered pharmacokinetics.

See the Herceptin Investigator’s Brochure for details on nonclinical and clinical studies.

1.2.1.4 Perjeta® (Pertuzumab)

Perjeta® (pertuzumab) is a fully humanized monoclonal antibody based on the human Ig G1(κ) framework sequences. It consists of two heavy chains (449 residues) and two light chains (214 residues). Similar to Herceptin, Perjeta is directed against the extracellular domain of HER2; however, it differs from Herceptin in the epitope-binding regions of the light chain (12 amino acid differences) and heavy chain (29 amino acid differences). As a result, Perjeta binds to an epitope within what is known as sub-domain 2 of HER2, whereas the epitope for Herceptin is localized to sub-domain 4 (Cho et al. 2003; Franklin et al. 2004).

Perjeta acts by blocking the dimerization of HER2 with other HER family members, including HER1 (EGFR), HER3, and HER4. As a result, Perjeta inhibits ligand-initiated intracellular signaling through two major signal pathways: MAP-kinase and PI3-K. Inhibition of these signaling pathways can result in growth arrest and apoptosis, respectively (Baselga 2010).

Because of the different binding sites of Perjeta and Herceptin, ligand-activated downstream signaling is blocked by Perjeta but not by Herceptin. Because of their complementary modes of action, the combination of Perjeta and Herceptin was shown to act synergistically in HER2-overexpressing diseases.

The efficacy of Perjeta was demonstrated in a multicenter, randomized, double-blind, placebo-controlled, Phase III study (WO20698/TOC4129g; CLEOPATRA) in patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who had not received previous anti-HER2 therapy or chemotherapy for metastatic disease. A total of 808 patients were enrolled at sites in 25 countries. The primary efficacy endpoint was IRF-assessed PFS. Key secondary efficacy endpoints included OS and Independent Review Facility (IRF)-assessed ORR.

In this Phase III study, CLEOPATRA, patients were randomized in a 1:1 ratio to Perjeta plus Herceptin plus docetaxel (Perjeta arm; n = 402) or placebo plus Herceptin plus docetaxel (placebo arm; n = 406). Perjeta was given by IV infusion at an initial dose of 840 mg, followed every 3 weeks thereafter by a dose of 420 mg. Placebo was given by IV infusion every 3 weeks. Herceptin was given by IV infusion at an initial dose of 8 mg/kg, followed every 3 weeks thereafter by a dose of 6 mg/kg. Docetaxel was given by IV infusion at an initial dose of 75 mg/m^2 every 3 weeks. The dose of docetaxel could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. Patients were treated with Perjeta/placebo and Herceptin until disease progression, withdrawal of consent, or unmanageable toxicity. Patients were treated with docetaxel for at least six cycles.

Demographic and baseline characteristics were generally well balanced between treatment groups.

At the time of the data cutoff for the primary analysis (13 May 2011), 433 IRF-confirmed PFS events had occurred in 242 patients (59.6%) in the placebo arm and 191 patients (47.5%) in the Perjeta arm.

Study WO20698/TOC4129g demonstrated a statistically significant and clinically meaningful improvement in IRF-assessed PFS in the Perjeta arm compared with the placebo arm (HR: 0.62; 95% CI: 0.51, 0.75; p < 0.0001), with an increase of 6.1 months in median PFS (12.4 months in the placebo arm vs. 18.5 months in the Perjeta arm). The Kaplan-Meier curve (see Figure 1; Baselga et al. 2012) shows an early separation beginning at the first tumor assessment (9 weeks), which is maintained from this point

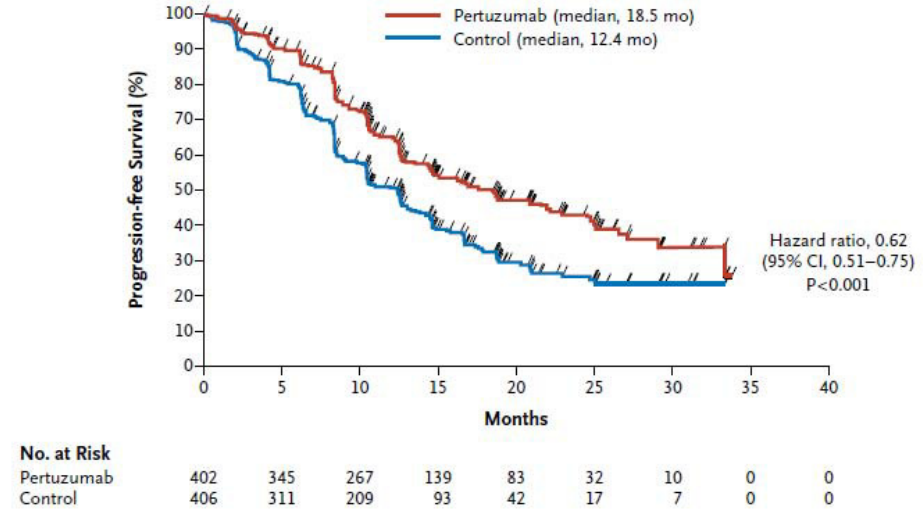
onward. Primary efficacy results for OS and IRF-assessed ORR supported the PFS benefit. Analyses of PFS by clinically relevant patient subgroups suggested that the benefit of Perjeta in combination with Herceptin and docetaxel was observed consistently in all prespecified subgroups tested, including those based on geographic region, prior treatment, age, race, presence of visceral disease, hormone receptor status, and HER2 IHC or fluorescent in situ hybridization (ISH) status.

After 1 year of additional follow-up (14 May 2012 data cutoff), the efficacy results (primary efficacy endpoint of IRF-assessed PFS) for Study WO20698/TOC4129g remained robust, confirming the results of the primary analysis and supporting the current labeling for Perjeta.

In addition, a second interim analysis of the secondary efficacy endpoint of OS achieved statistical significance. The main efficacy findings are as follows:

- The second interim analysis of OS crossed the predefined stopping boundary for statistical significance ($p \leq 0.0138$), demonstrating that treatment with Perjeta arm significantly improved OS compared with placebo arm (HR: 0.66; 95% CI: 0.52, 0.84; $p = 0.0008$). Thus, Study WO20698/TOC4129g met its OS endpoint (14 May 2012 data cutoff).
- Subgroup analyses of OS were consistent with the overall OS analysis (14 May 2012 data cutoff).
- An updated analysis of PFS (14 May 2012 data cutoff), on the basis of the investigator's assessment alone, demonstrated that the PFS benefit observed at the primary analysis was maintained after an additional year of follow-up. An HR of 0.69 and an increase of 6.3 months in median PFS (from 12.4 months in the placebo arm to 18.7 months in the Perjeta arm) were consistent with those from the primary analysis of IRF-assessed PFS (13 May 2011 data cutoff) and provide further confirmation of the positive benefit-risk ratio of treatment with Perjeta plus Herceptin plus docetaxel in patients with HER2-positive metastatic or locally recurrent unresectable breast cancer.
- Under a fixed-sequence testing hierarchy implemented for confirmatory testing of secondary endpoints (OS, IRF-assessed ORR), the updated results for IRF-assessed ORR were considered statistically significant (ORR: 69.3% in placebo + trastuzumab + docetaxel vs. 80.2% in Perjeta arm + trastuzumab + docetaxel; difference in response rates between treatment arms of 10.8; 95% CI: 4.2, 17.5; $p = 0.001$).

Figure 1 Independently Assessed Progression-Free Survival in Study TOC4129g/WO20698



mo = month; No. = number.

The combination of Perjeta and Herceptin IV plus docetaxel increased rates of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin compared with the control group. These adverse events were primarily Grades 1 and 2, manageable, and occurred during docetaxel therapy. There was no increase in cardiac adverse events or left ventricular systolic dysfunction (LVSD; Baselga et al. 2012).

LVSD, any grade, was reported more frequently in the control group than in the Perjeta group (8.3% vs. 4.4%, respectively). LVSD of Grade 3 or higher was reported in 2.8% of the patients in the control group and in 1.2% of the patients in the Perjeta group. Among patients in whom the LVEF was assessed at baseline and post-baseline, 6.6% of patients in the control group and 3.8% of patients in the Perjeta group had declines of ≥10% from baseline that resulted in an LVEF of <50% (Baselga et al. 2012).

In the placebo plus Herceptin plus docetaxel arm, 45.8% of patients experienced neutropenia and 7.6% experienced febrile neutropenia of Grade ≥3 compared with 48.9% and 13.8% of patients, respectively, in the Perjeta and Herceptin plus docetaxel arm (Baselga et al. 2012).

After an additional year of follow-up (14 May 2012 data cutoff), data from Study WO20698/TOC4129g indicate that the safety profile of Perjeta arm is essentially unchanged. Safety findings in the Perjeta arm remain comparable to those in the placebo arm, apart from a higher incidence of Grade 1 or 2 diarrhea, rash, mucosal inflammation, pruritus, dry skin, and Grade 3 or 4 febrile neutropenia. Although the

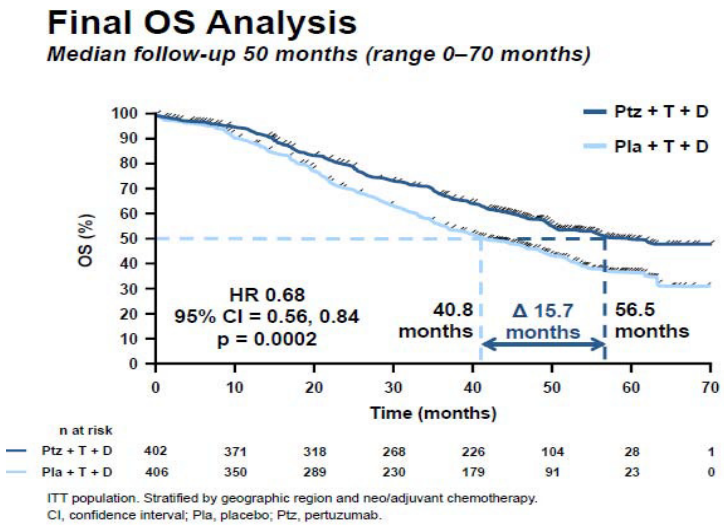
incidence of serious adverse events remained higher in the Perjeta arm (29.0% placebo arm vs. 36.3% Perjeta arm), the proportion of patients who discontinued therapy because of an adverse event or death was 9.0% in both treatment arms. The incidence of treatment-related deaths remained low in both arms (≤1.5% of patients) with no new treatment-related deaths reported in the Perjeta arm since the first data cutoff date.

Importantly, despite dual targeting of the same HER2-receptor pathway with an additional year of follow-up, the incidence and severity of cardiac toxicity in the Perjeta arm remained similar to those in the placebo arm. The incidence of cardiac adverse events (all grades) was 16.4% in the placebo arm and 14.5% in the Perjeta arm with LVSD (all grades) being the most frequently reported event (8.3% vs. 4.4% in the placebo and Perjeta arm).

Declines in LVEF by ≥10% points from baseline and to <50% were reported in 6.6% and 3.8% of patients in the placebo and Perjeta arms, respectively. Seventy-two percent (placebo arm) and 86.7% (Perjeta arm) of those patients recovered to a value ≥50%. The incidence of symptomatic LVSD was low, occurring in 1.8% (n=7) versus 1.0% (n=4) of patients in the placebo and Perjeta arms, respectively. In 8 out of 11 patients, the symptomatic LVSD had resolved at data cutoff (Swain et al. 2013a).

The results of the final OS analysis after a median follow-up of 50 months were presented at the European Society of Medical Oncology (ESMO) 2014; median OS has now been reached for patients receiving the Perjeta regimen. Adding Perjeta IV to Herceptin IV and docetaxel IV extended OS by 15.7 months compared with Herceptin and docetaxel (median OS: 56.5 vs. 40.8 months). The risk of death was reduced by 32% for patients who received the Perjeta regimen compared with those who received Herceptin IV and docetaxel (HR=0.68, 95% CI: 0.56, 0.84; p=0.0002). The OS results were consistent across patient subgroups. The median PFS improvement of more than 6 months was maintained (median PFS of 18.7 months for people who received Perjeta, Herceptin IV, and docetaxel compared with 12.4 months for those who received Herceptin IV and docetaxel). Patients who received the Perjeta regimen had a 32% reduction in the risk of their disease worsening or death (PFS; HR=0.68, 95% CI: 0.58, 0.80) compared with patients who received Herceptin and docetaxel. The safety profile of Perjeta was consistent with that observed previously in the CLEOPATRA study, including long-term cardiac safety. No new safety signals were observed.

Figure 2 Final Overall Survival Analysis



D = docetaxel; ESMO = European Society of Medical Oncology; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; Pla = placebo; Ptz = pertuzumab; T = trastuzumab.
S. Swain ESMO 2014

The incorporation of Herceptin SC in place of Herceptin IV in the standard of care regimen of Herceptin IV, Perjeta IV, and chemotherapy should have a low additional impact on tolerability and safety, and together with rigorous monitoring of the known toxicities of the agents involved, the proposed study poses an acceptable risk in this patient population with advanced breast cancer.

The complementary mechanisms and good tolerability profile of each of the HER2-directed antibodies, Herceptin and Perjeta, strongly supported by the results of the randomized, double-blind Phase III TOC4129g/WO20698 study, provide a strong rationale to further explore and better characterize the safety and tolerability profile of the combination of the anti-HER2 antibodies Herceptin and Perjeta given in combination with docetaxel.

See the Perjeta Investigator's Brochure for details on nonclinical and clinical studies.

1.2.2 Docetaxel

Taxanes are anti-neoplastic agents that bind to free tubulin within the cell and promote the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This mode of action leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, blocking cells in the M-phase of the cell cycle and leading to cell death. Extensive Phase II and Phase III data have led

to regulatory approvals for the use of docetaxel either in combination or as monotherapy for the treatment of breast cancer.

Docetaxel is a semi-synthetic analog of paclitaxel, which was the first taxane to be identified. Both Herceptin and Perjeta have been successfully administered with docetaxel in doses ranging between 60 mg/m^2 and 100 mg/m^2.

When administered with Herceptin and Perjeta, the recommended initial dose of docetaxel is 75 mg/m^2, administered thereafter on an every 3-week schedule. The dose of docetaxel may be escalated to 100 mg/m^2 at the investigator's discretion on subsequent cycles if the initial dose is well tolerated.

See the local prescribing information for docetaxel for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This is an open-label, single-arm, multicenter, Phase IIIb study with the primary objective to evaluate the safety and tolerability of Herceptin SC in combination with Perjeta IV plus docetaxel in patients with HER2–positive advanced (metastatic or locally recurrent) breast cancer. Improved PFS and OS, along with an acceptable safety profile, have been demonstrated in clinical trials of Perjeta in combination with Herceptin IV and docetaxel in this patient population (Study TOC4129g/WO20698). In parallel, the Phase III Study BO22227 demonstrated the non-inferiority of Herceptin SC compared with Herceptin IV in patients with EBC in the neoadjuvant and adjuvant settings. Combination therapy of Perjeta and Herceptin IV plus docetaxel has become the new standard of care for these patients. Since Herceptin SC has not been investigated in combination with Perjeta IV in patients with MBC, no safety and tolerability data are available, but the similar setup of the current study and CLEOPATRA (TOC4129g/WO20698) study (addendum CSR 1053649) will allow an indirect (historical) comparison of safety data results.

The present study will be conducted as a post-authorization safety measure to generate additional safety and tolerability data for Herceptin SC in combination with Perjeta IV and docetaxel in the HER2-positive advanced breast cancer setting, a triplet regimen that is approved and is the standard of care in this indication.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective for this study is to evaluate the safety and tolerability of Herceptin SC in combination with Perjeta IV plus docetaxel in patients with HER2–positive advanced (metastatic or locally recurrent) breast cancer.

- Overall safety profile as determined by adverse events of any grade of severity, and adverse events Grade ≥3 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0 and cardiac function will be assessed including the following: cardiac events Grade ≥ 3, congestive heart failure (CHF), and cardiac death (see Section 6.5)

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are to evaluate Herceptin SC in combination with Perjeta IV plus docetaxel with respect to:

- Efficacy parameters (see Section 6.4)

  PFS

  OS

  Objective Response Rate (ORR)

- Incidence of anti-Herceptin and anti-rHuPH20 antibody formation

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is an open-label, single-arm, multicenter, Phase IIIb study to evaluate the safety and tolerability of Herceptin SC in combination with Perjeta IV plus docetaxel (see Figure 3). Patients with HER2–positive advanced breast cancer (metastatic or locally recurrent) who have not previously received systemic non–hormonal anti-cancer therapy in the metastatic setting are eligible to participate in the study. Enrollment is defined as first dose of study drug administration.

Four hundred patients are planned to be enrolled into the study at approximately 110 centers worldwide. Details of the study treatment are given in Section 4.3.

Treatment Period

Every 3 weeks (21 days) the patient will receive Herceptin SC (fixed dose of 600 mg/5 mL), Perjeta IV (loading dose of 840 mg followed by 420 mg on Day 1 of each subsequent cycle), and docetaxel IV (at least six cycles with recommended initial dose of 75 mg/m^2). After Cycle 6, continuation of docetaxel treatment is at the discretion of the treating physician in agreement with the patient. The dose of docetaxel may be escalated to 100 mg/m^2 at the investigator's discretion on subsequent cycles if the initial dose is well tolerated.

End of Treatment

End of treatment for each patient is defined as receiving study medication until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end, whichever occurs first.

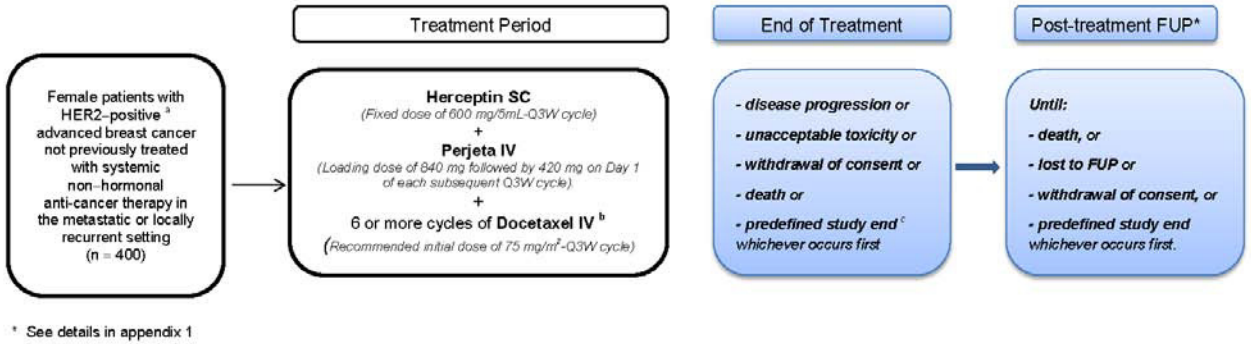
Post-Treatment Follow-up

If the patient discontinues all study treatments because of unacceptable toxicity, she will enter in follow-up and will have tumor assessments every 9 weeks (±3 days) until disease progression or predefined end of the study (see Section 3.2), whichever occurs first.

In addition, patients with disease progression will continue to be followed until death, loss to follow-up, withdrawal of consent, predefined study end (see Section 3.2), or study termination by Roche.

A Schedule of Assessments is provided in Appendix 1.

Figure 3 Study Design



FUP = follow-up; HER2 = human epidermal growth factor receptor 2; IV = intravenous; Q3W = every 3 weeks; SC = subcutaneous.

See Table 1 for dose administration guidelines.

[a] Defined as either immunohistochemistry 3+ or in situ hybridization positive.

[b] After Cycle 6, continuation of docetaxel treatment is at the discretion of the treating physician in agreement with the patient. The dose of docetaxel may be escalated to 100 mg/m^2 at the investigator's discretion on subsequent cycles if the initial dose is well tolerated.

[c] Cutoff of Final Safety Analysis will occur 24 months after the last patients is recruited (see Section 3.2).

3.1.1 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will be established for the study with Roche members who are independent from the BO29159 study team. The IMC membership will include representatives from clinical science, safety science, and biostatistics. Specific policies on the operation of the IMC will be documented in an IMC Charter.

The IMC will meet on a regular basis over the course of the study, with the first review when 50 patients are treated for at least 3 cycles, and annually thereafter, as specified in the IMC Charter. The IMC may also meet on an unscheduled basis if any unexpected safety concerns arise.

The details of the IMC will be provided in a separate IMC Charter document.

3.2 END OF STUDY

The primary objective of this study is the safety outcome. The study will end at the time of the cutoff for the final analysis, **24 months** after the last patient has been enrolled, or all patients in the study have withdrawn consent, died, or if the study is prematurely terminated by the Sponsor, whichever occurs first.

All patients who are still receiving study treatment at time of cutoff for the final analysis will have their post-treatment safety follow-up visit 28–35 days after the last dose of study treatment, and then will be considered as finished with their participation in the study; these patients will continue to be followed in accordance with the local standard of care.

These patients may be provided with commercial drug for continuation of treatment. This will depend on the local availability of commercial Herceptin SC, Herceptin IV, and Perjeta.

The post-study adverse events (see Section 5.6) should be reported directly to Roche Safety Risk Management and not on the eCRF. This data collection will be restricted to reporting of serious adverse events that are believed to be related to study drug treatment.

3.3 RATIONALE FOR STUDY DESIGN

This is an open-label, single-arm, multicenter, Phase IIIb study with the primary objective to evaluate the safety and tolerability of Herceptin SC in combination with Perjeta IV plus docetaxel in patients with HER2–positive advanced (metastatic or locally recurrent) breast cancer. Improved PFS and OS, along with an acceptable safety profile, have been demonstrated in clinical trials of Perjeta in combination with Herceptin IV and docetaxel in this patient population (Study TOC4129g/WO20698). In parallel, the Phase III Study BO22227 demonstrated the non-inferiority of Herceptin SC compared with Herceptin IV in patients with EBC in the neoadjuvant and adjuvant settings. Combination therapy of Perjeta and Herceptin IV plus docetaxel has become the new

standard of care for these patients. Since Herceptin SC has not been investigated in combination with Perjeta in patients with MBC, no safety and tolerability data are available, but the similar setup of the current study and CLEOPATRA (TOC4129g/WO20698) study (addendum CSR 1053649) will allow an indirect (historical) comparison of safety data results.

As this is a safety study where all patients must receive the active treatment, the study design will be open-label and non-randomized.

Safety and tolerability will be carefully evaluated, and the type of data collected and the frequency with which patients are monitored will ensure the safety of the patients at all times, as well as fulfill local and international regulatory requirements.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

Efficacy outcome measures (secondary objectives) for this study are to evaluate Herceptin SC in combination with Perjeta IV plus docetaxel with respect to:

- PFS based on investigator assessment is defined as the time from first dose of study drug administration to the first radiographically documented progression of disease, as determined by the investigator using current Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (see Appendix 5; Eisenhauer et al. 2009) or death from any cause, whichever occurs first. Carcinomatous meningitis diagnosed by cytologic evaluation of cerebral spinal fluid will also define PD. Medical photography will also be allowed to monitor chest wall recurrences of subcutaneous lesions.
- OS is defined as the time from the date of first dose of study drug administration to the date of death from any cause.
- ORR is defined as a complete response (CR) or partial response (PR) determined by the investigator using RECIST v1.1 (see Appendix 5; Eisenhauer et al. 2009) on two consecutive occasions ≥4 weeks apart. Patients with disease localized only to the bone will not be included in the analysis of objective response.

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events Grade ≥3
- Incidence and severity of all serious adverse events
- Incidence and severity of all adverse events
- Incidence of CHF and cardiac death
- LVEF over the course of the study and decline in LVEF from baseline
- Cause of death while in the study
- Incidence of adverse events leading to discontinuation

- Incidence of adverse events leading to dose modification
- Clinically relevant laboratory test abnormalities (see Section 5.3.5.5 for details)
- Incidence of anti-Herceptin and anti-rHuPH20 antibodies

Grading of non-serious and serious adverse events is performed according to NCI CTCAE, v4.0, (published 28 May 2009 and v4.03: 14 June 2010). Heart failures will also be classified according to the New York Heart Association (NYHA) functional classification system (Weatherall et al. 1996; see Appendix 4).

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population for this study is patients with HER2–positive advanced (metastatic or locally recurrent) breast cancer without previous systemic non-hormonal anti-cancer therapy for the metastatic or locally recurrent disease.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry according to the timing specified in the Schedule of Assessments (see Appendix 1):

1. Signed, written informed consent approved by the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC)
2. Female patients aged 18 years or older
3. Histologically or cytologically confirmed and documented adenocarcinoma of the breast with metastatic or locally recurrent disease not amenable to curative resection. Patients with measurable and/or non-measurable disease evaluable according to RECIST v1.1 (see Appendix 5) are eligible.

   Notes:

   - Patients with only bone metastases are eligible provided that they have some bone metastases that have not been previously irradiated and tumor tissue samples from the primary tumor are available for local HER2 testing.
   - Locally recurrent disease must not be amenable to resection with curative intent.
   - Patients with de novo Stage IV disease are eligible.
4. HER2-positive disease (defined as either IHC 3+ or ISH positive) as assessed by local laboratory on primary tumor or metastatic site if primary tumor not available (positive ISH is defined as a ratio of ≥ 2.0 for the number of HER2 gene copies to the number of signals for CEP17, or for single probe tests, a HER2 gene count > 4).
5. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 (see Appendix 3)
6. LVEF of at least 50%

7. Negative serum pregnancy test result in women of childbearing potential (WOCBP; defined as premenopausal or $<$12 months of amenorrhea postmenopause and who have not undergone surgical sterilization)
8. WOCBP must agree to use a highly effective, non-hormonal form of contraception (such as surgical sterilization) or two effective forms of non-hormonal contraception or true abstinence during the treatment period and for at least 7 months after discontinuation of study treatment (see Section 5.1.4, Pregnancy, for details).
9. Life expectancy of at least 12 weeks

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry. Assessments must be performed according to the timing specified in the Schedule of Assessments (see Appendix 1):

1. Previous systemic non-hormonal anti-cancer therapy for the metastatic or locally recurrent disease. Note: Prior to study entry, up to two lines of hormonal therapy for metastatic or locally recurrent disease are permitted, one of which may be in combination with everolimus.
2. Disease-free interval of $less\ than$ 6 months from completion of adjuvant or neoadjuvant systemic non-hormonal treatment to recurrence of breast cancer
3. Previous approved or investigative anti–HER2 agents as neoadjuvant or adjuvant therapy for any breast cancer treatment, except Herceptin
4. History of persistent Grade 2 or higher hematological toxicity resulting from previous adjuvant or neoadjuvant therapy
5. Patients with radiographic evidence of CNS metastases as assessed by computed tomography or magnetic resonance imaging (MRI) that are not well controlled (i.e., are symptomatic or require control with continuous corticosteroid therapy [e.g., dexamethasone]). Note: Patients with CNS metastases are permitted to participate in the study if they have been stable in the 3 months prior to screening (as assessed by the investigator) after receiving local therapy (irradiation, surgery, etc.) but have not received anti-HER2 therapy.
6. Current peripheral neuropathy of Grade 3 or greater
7. History of other malignancy within the last 5 years prior to first dose of study drug administration (dosing), except for carcinoma in situ of the cervix or basal cell carcinoma
8. Inadequate organ function, evidenced by the following laboratory results:
   a) ANC $<$1500 cells/mm^3
   b) Platelet count $<$100,000 cells/mm^3
   c) Hemoglobin $<$9 g/dL
   d) Total bilirubin greater than the upper limit of normal (ULN; unless the patient has documented Gilbert's syndrome)
   e) AST (SGOT) or ALT (SGPT) $>2.5\times$ ULN

f) AST (SGOT) or ALT (SGPT) $>1.5\times$ ULN with concurrent serum alkaline phosphatase $>2.5\times$ ULN. Serum alkaline phosphatase may be $>2.5\times$ ULN only if bone metastases are present and AST (SGOT) and ALT (SGPT) are $<1.5\times$ ULN

g) Serum creatinine >2.0 mg/dL or 177 µmol/L

h) INR and aPTT or PTT $>1.5\times$ ULN (unless on therapeutic anticoagulation)

9. Uncontrolled hypertension (systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg) with or without medication
10. Clinically significant cardiovascular disease as follows:
    a) Cerebrovascular accident/stroke or myocardial infarction within 6 months prior to first study medication, or
    b) Unstable angina, or
    c) History of or active CHF of any NYHA criteria, or
    d) History of or ongoing serious cardiac arrhythmia requiring medication (except controlled atrial fibrillation or paroxysmal supraventricular tachycardia)
11. History of LVEF decline to below 50% during or after prior Herceptin neoadjuvant or adjuvant therapy
12. Current known infection with HIV, hepatitis B virus, or hepatitis C virus
13. Severe uncontrolled concomitant disease that would contraindicate the use of any of the investigational drugs used in this study or that would put the patient at high risk for treatment-related complications: such as uncontrolled systemic disease (e.g., pulmonary [including interstitial lung disease]) or metabolic disease, wound healing disorders, ulcers, or bone fractures
14. Pregnant or lactating women
15. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy
16. Major surgical procedure or significant traumatic injury within 14 days prior to first dose of study drug administration (dosing) or anticipation of need for major surgery during the course of study treatment. Note: Should surgery be necessary during the course of the study, patients should be allowed to recover for a minimum of 14 days prior to subsequent study treatment.
17. Receipt of IV antibiotics for infection within 14 days prior to first dose of study drug administration
18. Current chronic daily treatment (continuous for >3 months) with corticosteroids (dose ≥ 10 mg/day methylprednisolone), excluding inhaled steroids
19. Known hypersensitivity to any of the study medications or to excipients of recombinant human or humanized antibodies
20. History of receiving any investigational treatment within 28 days prior to first dose of study drug administration (dosing)

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21. Assessed by the investigator as unable or unwilling to comply with the requirements of the protocol
22. Concurrent participation in any interventional clinical trial

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Not applicable; this is an open-label, non-randomized single-arm study.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

Study drug packaging will be overseen by the Sponsor's Clinical Trial Supplies department and bear a label with the identification required by local law, the protocol number, drug identification, and dosage.

The packaging and labeling of the study drug will be in accordance with Sponsor standards and local regulations.

The study drug must be stored according to the details on the Product Information. The drug label indicates the storage temperature.

Local packaging in some countries may be different.

Upon arrival of investigational products at the site, site personnel should check them for damage, verify proper identity, quantity, integrity of seals, and temperature conditions and report any deviations or product complaints upon discovery.

4.3.1.1 Subcutaneous Herceptin

Herceptin for SC administration will be supplied in a vial, ready-to-use liquid formulation with a nominal content of 600 mg/5 mL Herceptin. The drug product contains rHuPH20, histidine/histidine-HCl (buffer), α,α-trehalose dehydrate (bulking agent), methionine (stabilizer), and polysorbate 20 (stabilizer/emulsifier) in water for injection at a pH of 5.5 ± 0.6. rHuPH20, the human recombinant hyaluronidase (manufactured in a Chinese hamster ovary cell line), is a permeation enhancer to allow SC administration of higher volumes.

The recommended storage conditions are 2–8°C, protected from light. Batch-specific details and information on shelf life are given in the packaging label.

For further details, see the Herceptin Investigator's Brochure.

4.3.1.2 Intravenous Perjeta

Perjeta IV will be supplied by the Sponsor to the investigational sites.

Perjeta drug product is provided as a single-use formulation containing 30 mg/mL Perjeta in 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose, and 0.02% polysorbate 20. Each 20-mL vial contains 420 mg of Perjeta (14.0 mL/vial).

Upon receipt, Perjeta vials are to be refrigerated at 2–8°C (36–46°F) until use. Perjeta vials should not be used beyond the expiration date provided by the manufacturer. Because the formulation does not contain a preservative, the vial seal may be punctured only once. Any remaining solution should be discarded. Vial contents should be protected from light and should not be frozen.

For further details, see the Perjeta Investigator's Brochure.

4.3.1.3 Intravenous Docetaxel

Commercial docetaxel for IV administration will be obtained locally by the investigational sites.

For further details, see the local prescribing information for docetaxel and/or recognized clinical practice guidelines.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Subcutaneous Herceptin

A fixed dose of 600 mg/5 mL Herceptin SC, irrespective of the patient's weight, will be administered throughout the treatment phase. All doses of Herceptin SC will be administered as an SC injection into the thigh by a trained health care professional over a period of 2–5 minutes. New injections should be given at least 2.5 cm from the old injection site(s) and never into areas where the skin is red, bruised, tender, or hard. During the course of treatment with Herceptin SC, other medicinal products for SC administration should preferably be injected at different sites. Patients should be observed for 6 hours after the first injection and for 2 hours after subsequent injections for signs or symptoms of ARRs.

Significant injection-related symptoms must have been resolved before any subsequent study treatment administration. Patients who experience injection-related symptoms may be premedicated with paracetamol and antihistamines for subsequent injections. Dose reductions for toxicity are not permitted.

The medicinal products should be administered sequentially on Day 1 of each cycle (every 3 weeks; see Table 1) as follows: Herceptin SC first, then Perjeta IV, and then docetaxel IV.

Herceptin SC administration may be delayed to assess or treat adverse events, such as cardiac adverse events, myelosuppression, or other events. No dose reduction will be allowed for Perjeta IV or Herceptin SC (see Section 5.1.1).

4.3.2.2 Intravenous Perjeta

Perjeta will be administered as an IV infusion on Day 1 of the first treatment cycle as a loading dose of 840 mg, followed by 420 mg on Day 1 of each subsequent 3-week cycle. Perjeta IV should be administered 60 minutes after the end of Herceptin SC administration. An observation period of 30–60 minutes is recommended after each Perjeta infusion.

Initial infusions of Perjeta will be administered over 60 (±10) minutes and patients will be observed for an additional 60 minutes from the end of infusion for infusion-associated symptoms such as fever, chills, etc. Interruption or slowing of the infusion may reduce such symptoms. If the infusion is well tolerated, subsequent infusions may be administered over 30–60 (±10) minutes with patients observed for an additional 30 minutes from the end of the infusion for infusion-associated symptoms.

Perjeta IV administration may be delayed to assess or treat adverse events such as cardiac adverse events, myelosuppression, or other events. No dose reduction will be allowed for Perjeta IV or Herceptin SC (see Section 5.1.1).

In the case of surgery during the study, there is no evidence that HER2 antibodies delay wound healing, but patients should have recovered from surgery and anesthesia (this includes liver function values) for a minimum of 14 days before antibody treatment.

4.3.2.3 Intravenous Docetaxel

Docetaxel will be administered in line with the respective product information and/or recognized clinical practice guidelines. It will be administered **after** Herceptin SC and Perjeta IV (see Table 1 and Sections 4.3.2.1 and 4.3.2.2).

When administered with Herceptin and Perjeta, the recommended initial dose of docetaxel is 75 mg/m^2, administered thereafter on a 3-week cycle. The dose of docetaxel may be escalated to 100 mg/m^2 at the investigator's discretion on subsequent cycles if the initial dose is well tolerated.

On or prior to Cycle 6, docetaxel should only be discontinued for PD or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment is at the discretion of the treating physician in agreement with the patient.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.1.4.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Table 1 Summary of Study Treatment Dose and Schedule

Cycle [a]	Herceptin SC	Perjeta IV	Docetaxel IV
Cycle 1	Day 1: A fixed dose of **600 mg/5 mL** Herceptin SC administered over 2–5 minutes	Day 1: Perjeta IV administration **60 minutes** after the end of the Herceptin SC administration **840 mg loading dose,** administered over 60 minutes	Day 1: Docetaxel IV administration **60 minutes** after the end of the Perjeta IV administration **75 mg/m^2** administered over 60 minutes Cycle 1
	Patients to be observed **for 6 hours after the first injection of Herceptin SC**	Followed by a 60-minute observation period after the first Perjeta IV administration	Observe according to institution standards for docetaxel IV administration
From Cycle 2	Day 1: A fixed dose of **600 mg/5 mL** Herceptin SC, administered over 2–5 minutes	Day 1: Perjeta IV administered **60 minutes** after the end of the Herceptin SC administration **420 mg dose** administered over 60 minutes (or 30–60 minutes if well tolerated)	Day 1: Docetaxel IV administered **30–60 minutes** after the end of the Perjeta IV administration **75 mg/m^2 (or 100 mg/m^2)[b]** administered over 60 minutes
	Patients to be observed for **2 hours after subsequent injections of Herceptin SC**	Followed by a 30 to 60-minute observation period after the subsequent Perjeta IV administration	Observe according to institution standards for docetaxel IV administration

IV = intravenous; SC = subcutaneous.

[a] One cycle every 3 weeks (21 days).

[b] Docetaxel IV for at least 6 cycles: After Cycle 6, continuation of docetaxel treatment is at the discretion of the treating physician and in agreement with the patient.

Prior to disease progression, if a study patient is unable to tolerate:

- Docetaxel IV, then it is possible to continue treatment with Herceptin SC and Perjeta IV per study protocol until disease progression, or
- Perjeta IV, then it is possible to continue treatment with Herceptin SC and docetaxel IV per study protocol until disease progression, or
- Herceptin SC, then it is possible to continue treatment with docetaxel IV only per study protocol (Perjeta IV treatment to be stopped when Herceptin SC treatment is stopped) until disease progression or to switch to a non-study protocol standard of care treatment regimen (i.e., Herceptin IV, Perjeta IV, docetaxel IV, etc.)

The above options are to be based on the investigator's assessment of the patient's potential benefit relative to the risk and in the best interest of the study patient.

The Herceptin SC dose and Perjeta IV dose are fixed doses and do not need to be adjusted for body weight.

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4.3.3 Investigational Medicinal Product Accountability

Herceptin SC and Perjeta IV are considered to be investigational medicinal products (IMPs) in this study.

Docetaxel IV is considered to be a non-IMP in this study.

All IMPs required for completion of this study (Herceptin SC and Perjeta IV) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMP through use of the interactive voice/Web response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs and non-IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Subcutaneous Herceptin

All patients will be treated until predefined study end (see Section 3.2), disease progression, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

All patients who are still receiving study treatment at time of cutoff for the final analysis will have their post-treatment safety follow-up visit 28–35 days after the last dose of study treatment, and then will be considered as finished with their participation in the study; these patients will continue to be followed in accordance with the local standard of care.

The post-study adverse events (see Section 5.6) should be reported directly to Roche Safety Risk Management and not on the eCRF.

These patients may be provided with commercial drug for continuation of treatment. This will depend on the local availability of commercial Herceptin and Perjeta.

The Sponsor will offer post-trial access to the study drug Herceptin and Perjeta free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for HER2-positive advance breast cancer (metastatic or locally recurrent)
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for HER2-positive advance breast cancer (metastatic or locally recurrent)
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf.

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 28 days prior to the first dose of study drug administration to the study completion/early termination visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. Concomitant surgeries and procedures will be captured on separate dedicated eCRFs.

Patients should receive full supportive care when necessary, including transfusion of blood and blood products, antibiotics, etc., according to standard of care.

All protocol-allowed medications that are taken by the patient for concomitant disease(s) should be continued as necessary during the study and be recorded on the eCRF. The following list of allowed medications is provided as guidance. Treatments prescribed to patients should be adapted according to the local standard of care practice.

The following treatments/procedures are permitted:

- Paracetamol (acetaminophen) or other analgesics and diphenhydramine, chlorpheniramine, or other antihistamines can be used according to local clinical practice for the prevention and treatment of infusion reactions associated with Perjeta and/or Herceptin
- Medication to treat diarrhea (e.g., loperamide)
- Granulocyte colony stimulating factor (G-CSF) may be used according to the product license and according to the currently approved prescribing information for docetaxel and American Society of Clinical Oncology clinical guidelines (Smith et al. 2006).
- Steroids for docetaxel premedication and anti-emetics according to routine practice at each clinical site
- Inhaled steroids for asthma
- Bisphosphonates or a RANK ligand inhibitor may be given according to their product license and routine clinical practice at the investigator's discretion. Note: If these medications should be started during the trial, the patients must be assessed first for evidence of disease progression.
- Palliative surgical procedures. Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings. In the case of surgery during the study, patients should have recovered from surgery and anesthesia (this includes liver function) for a minimum of 14 days before antibody treatment.
- As a precautionary measure, it is recommended but not strictly required that if patients require placement of a central venous access device (CVAD), the procedure should be done 7 days prior to first study treatment start. The date of CVAD placement should be noted in the medical record and recorded in the eCRF. Episodes of CVAD replacement should be recorded, as should CVAD-related thrombosis, infection, or dysfunction.
- Anticoagulation therapy for maintenance of patency of permanent indwelling IV catheters is permitted.
- Palliative radiotherapy. Radiotherapy is only allowed during the study treatment period for the indication of bone or breast lesions present at baseline as long as the lesion is not a target lesion. If a patient requires radiation therapy to a new lesion, that new lesion would, per RECIST, qualify as PD.
- Approved endocrine therapies only after discontinuation of chemotherapy

4.4.2 Prohibited Therapy

The following treatments are not permitted:

- Treatment with other systemic anti-cancer agents (e.g., chemotherapy, immunotherapy) or other treatments not part of the protocol-specified anti-cancer therapy. Note: Approved endocrine maintenance therapies will be permitted only after discontinuation of chemotherapy.

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- Any oral, injected, or implanted hormonal methods of contraception
- Concurrent investigational agents of any type
- Initiation of herbal remedies for cancer treatment. Herbal remedies initiated prior to study entry and continuing during the study are permitted and must be reported on the appropriate eCRF.

The following treatments should be avoided because of the risk of immunosuppression:

- Chronic or high-dose oral corticosteroid therapy
- Tumor necrosis factor–α inhibitors
- Anti–T-cell antibodies

4.5 STUDY ASSESSMENTS

Details of the timing of assessments are presented in the Schedule of Assessments (see Appendix 1).

4.5.1 Informed Consent Form and Screening Log

Written informed consent for participation in the study (approved by the relevant IRB or IEC) must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening test and evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria within 28 days prior to the first administration of study medication (dosing), unless the procedures have already been conducted during this time period as part of the patient's routine clinical care. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), childbearing potential, and all medications used by the patient within 28 days prior to the first administration of study medication (dosing).

Women of childbearing potential are defined as premenopausal women and for women $<$12 months after the onset of menopause, unless they have undergone surgical sterilization.

The following criteria will be used to define postmenopause:

- No spontaneous menses for at least 12 months prior to study entry (e.g., spontaneous or secondary to hysterectomy) AND with a documented estradiol level in the postmenopausal range according to local institutional/laboratory standard, or

- A prior documented bilateral oophorectomy

Women failing to meet one of these criteria will be classified as premenopausal.

Demographic data will include age, sex, race, and self-reported ethnicity.

4.5.3 Physical Examination and Vital Signs

Physical examination and vital signs (pulse rate, blood pressure, body temperature), height, and weight will be measured at baseline. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

During the treatment period, a window of ±3 days of scheduled treatment will apply to all visits. Physical examination and vital signs (pulse rate, blood pressure, body temperature recorded again after infusion during observation period, and weight) will be measured before every administration of study treatment and at post-treatment safety follow-up visit. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Particular care will be taken with regard to cardiovascular signs and symptoms (jugular venous pressure, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.).

If applicable, vital sign assessments will be done during follow-up phase until disease progression (see Appendix 1).

4.5.4 Performance Status

Performance Status will be measured using the ECOG Performance Status scale (see Appendix 3).

It is recommended, where possible, that a patient's Performance Status will be assessed by the same person throughout the study.

Performance Status will be assessed at:

- Baseline
- Every three cycles of monoclonal antibody treatment
- 28-days post-treatment safety follow-up visit
- If applicable, at each follow-up visit until disease progression

4.5.5 Tumor and Response Evaluation

Screening tests and evaluations will be performed within **28 days** prior to the first administration of study medication (dosing), unless the procedures have already been conducted during this time period as part of the patient's routine clinical care.

Primary Tumor Receptor Status at Screening

HER2 Status: Patients must have HER2-positive status established prior to entering the study. Demonstrated evidence from previous testing is acceptable; otherwise HER2-positive status on fixed tissue blocks from the primary tumor (and/or metastatic site if primary tumor not available) will be assessed locally by IHC and/or ISH according to institutional criteria.

Hormone receptor status from primary tumor (and/or metastatic site if primary tumor not available) would be also reported.

Tumor Assessments Methodology

RECIST v1.1 will be used to evaluate response and assess PD (a summary of RECIST v1.1 is provided in Appendix 5).

The minimum screening examination should be done within 28 days before the first dose of study drug administration and should include:

- CT or MRI scan of the chest and abdomen (including liver, spleen, and adrenals) and pelvic scans. CT scans of the neck should be included if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if PD is suspected. PET scans will not be considered for assessment of efficacy at any time during the study (except as specified for bone scans in the absence of radioactive isotopes).
- CT scans should be performed with a contrast agent. The CT portion of a combination PET/CT scan is generally not performed with contrast; therefore, PET/CTs are generally not acceptable. However, if the site has acquired a high quality diagnostic CT scan, including the application of contrast agent (which may be performed with modern PET/CT scanners), the CT scan portion may be adequate for submission and evaluation. For patients with known allergies to the contrast media, it is acceptable to perform a chest CT scan without contrast and an MRI scan for the abdomen (ideally at baseline and every tumor assessment thereafter).
- CT or MRI scan of the brain and/or spine where there is clinical suspicion of CNS metastases and during the study if clinically indicated
- In case of suspicion of bone metastases, an isotope bone scan (with bone X-ray[s] as necessary) will be done at baseline. In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastases. Skeletal survey with plain X-ray is acceptable if there is no suitable alternative. It should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the appearance of new bone lesions.
- Medical photography to monitor chest wall recurrences (i.e., subcutaneous skin lesions)

All **measurable disease** must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor response will be assessed by the investigator on the basis of CT or MRI scans and (if indicated) isotope bone scan using RECIST v1.1 (see Appendix 5). An objective response is recommended to be confirmed by repeat assessments ≥4 weeks after initial documentation. Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions.

For patients with **non-measurable disease only**, qualitative evaluation of the burden of non-measurable disease with reproducible imaging techniques will be required at the fixed timepoints in the protocol. In such cases, response to treatment should be assessed as meaningful change in the tumor burden defined as persistence, disappearance, or unequivocal progression of the tumor as per RECIST.

Consistency of consecutive CT scans, X-rays, or MRIs should be ensured during all assessments for each patient with the same technique being used for evaluating lesions throughout the treatment period (use of spiral CT or MRI is required for baseline lesions <20 mm and must be documented in medical records and used consistently throughout the study). The use of oral and IV contrast, etc. should, as long as it is clinically possible, be kept consistent. Tumor measurements should be made by the same investigator/radiologist for each patient during the study to the extent that this is feasible. In case of clinically measurable superficial (such as skin) lesions, repeated photographs should be used to document tumor response. These photographs must include a ruler for documentation purposes.

Tumor response needs to be confirmed a minimum of 4 weeks after the initial response was noted or at the next scheduled tumor assessment if it is to occur more than 4 weeks after the initial response.

See the RECIST v1.1 (Appendix 5) for further details of criteria for differentiating between response, SD, and PD.

Summary of Scheduling of Tumor Assessments

Baseline total tumor burden must be assessed within a maximum of 28 days before first dose of study drug treatment (see above for the details of minimum screening examination).

Post-baseline assessments are to be performed every 9 weeks (±3 days) from the date of first dose of study drug administration) until disease progression or end of the study, whichever occurs first. All patients should have a minimum of a chest CT scan and abdominal CT scan. PET scans will not be considered for assessments of efficacy at any time during the study (except as specified for bone scans in the absence of radioactive isotopes). If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed. If a tumor assessment must be performed early or late,

subsequent assessments should be conducted according to the original schedule of every 9 weeks (±3 days) from the date of first dose of study drug administration.

All tumor assessments after baseline will be done within 3 days of the scheduled visit. If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment, unless signs of clinical progression are present.

4.5.6 Cardiac Assessments

Left Ventricular Ejection Fraction Assessment

LVEF will be assessed during the screening period within 6 weeks prior to first dose of study drug and every three treatment cycles by either echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan (with ECHO as the preferred method).

Patients will be re-assessed **with the same technique** used for baseline cardiac evaluation throughout the study and, to the extent possible, the assessments should be obtained at the same institution for an individual patient.

Electrocardiograms

A standard 12-lead ECG recording must be obtained at screening within 6 weeks prior to first dose of study drug and every three cycles during the treatment period at the time of LVEF measurement.

ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for ≥10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversations) should be avoided during the pre-ECG resting period and during ECG recording.

ECGs should be performed prior to any scheduled vital sign measurements and blood draws.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. Where available, digital recordings will be stored at the site.

ECG characteristics, including heart rate, RR, QRS duration, PR, and QT intervals, changes in T-wave morphology, and overall ECG interpretation, will be monitored by the investigator or designee and, if clinically significant, will be reported as adverse events according to standard grading, classification, and reporting guidelines.

These cardiac assessments (standard 12-Lead ECG & LVEF) will occur:

- At screening within 6 weeks prior to the first dose of study drug

- During treatment phase at the same time every three cycles and within 7 days prior to drug administration. The same technique must be used for baseline cardiac evaluation and throughout the study.
- At the post-treatment follow-up visit (28–35 days) after the last dose of study drug
- After post-treatment follow-up visit, only LVEF will be assessed (see details in Appendix 1).

4.5.7 Laboratory Assessments

Baseline assessments have to be done prior to the first administration (Day 1).

Samples for laboratory tests will be assessed locally.

Hematology and biochemistry will be done as part of regular safety assessments at baseline (within 3 days prior to the first dose of study drug), every treatment cycle, and 28 days after the last dose of study treatment. Assessments must be performed at each cycle within 3 days (with results available) prior to the administration of study drug.

Specifically, the following will be assessed:

- Hematology: hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and other cells)
- Biochemistry: sodium, potassium, calcium, chloride, magnesium, blood urea nitrogen, total protein, albumin, alkaline phosphatase, ALT, AST, gamma glutamyl transferase, LDH, total bilirubin, creatinine, blood glucose, and calculated creatinine clearance at baseline
- Coagulation: INR and aPTT or PTT. Tests should be repeated at each treatment cycle in all patients receiving therapeutic doses of anticoagulants.

Pregnancy test:

All WOCBP (premenopausal women and for women $<$12 months after the onset of menopause, unless they have undergone surgical sterilization) will have a **serum pregnancy test** at a local laboratory within 7 days prior to the first administration of study medication with result available at dosing.

For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential.

Urine pregnancy tests should be repeated during the treatment period

- Within 7 days prior to every third treatment cycle with result available at dosing starting at Cycle 3 (and as clinically indicated)
- At the post-treatment safety follow-up visit (28–35 days) after the last dose of study drug
- About 4 months and 7 months (during the closest follow-up visit) after discontinuation of study treatment until predefined end of the study (see Section 3.2)

Any positive urine pregnancy test result must be confirmed with a serum β-HCG evaluation at the local laboratory. Pregnancy test results must be available prior to the next scheduled study treatment. Women who have undergone surgical sterilization or are postmenopausal are exempt from pregnancy assessments.

WOCBP who are sexually active must agree to use a highly effective, non-hormonal form of contraception or two effective forms of non-hormonal contraception (see details in Section 5.1.4) during the study treatment and for at least 7 months after study treatment.

Unless otherwise specified, baseline tests and evaluations (e.g., physical examination) may be performed within 7 days prior to first dose of study drug administration, after confirmation of other eligibility criteria, unless the procedures have already been conducted during this time period as part of the patient's routine clinical care.

4.5.8 Herceptin Serum Concentration Assessments

The concentration of Herceptin will be characterized by measuring Herceptin with use of a validated method. Herceptin serum concentration will be assessed for all patients treated with Herceptin. The concentration of Herceptin will be used as part of the immunogenicity assessment.

The purpose of immunogenicity testing is to determine whether anti-drug antibodies (ADAs) against Herceptin or anti-rHuPH20 antibodies develop and whether these impact upon safety or efficacy. Blood sampling for immunogenicity testing will be done as per visiting schedule. All patients will be evaluated for antibodies against Herceptin and rHuPH20:

- At baseline,
- During treatment: at Cycle 2 prior to Herceptin SC drug administration, and
- During post-treatment follow-up phase: 28–35 days after the last dose of study drug and before the start of any subsequent line of treatment.

Plasma (for anti-rHuPH20 antibodies) and serum (for anti-Herceptin antibodies) samples will be shipped to a central laboratory on a continual basis. Details of sampling, storage, and shipping are described in the study's Sample Handling and Logistics Manual.

A three-tiered analytical testing approach will be performed for ADAs against both Herceptin and rHuPH20. A validated antibody-bridging ELISA will be used to screen for and confirm the presence of ADAs in patient samples, as well as to characterize and determine the titer of confirmed ADA-positive.

All immunogenicity samples will be analyzed centrally. Samples will be kept for retesting (if required) at the central laboratory and will be destroyed no later than 5 years after all study data have been collected.

See Appendix 1 for the schedule of screening and baseline assessments.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients' reason for discontinuation. The primary reason for withdrawal from the study should be documented on the appropriate eCRF section. At the time of withdrawn consent of the patient, two options will be given to her:

- Stop the study treatment but still allow survival data collection only, until predefined end of the study
- Stop the study treatment with no further data collection.

Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue all study drugs if they experience any of the following:

- Pregnancy
- Clinical signs and symptoms that are suggestive of symptomatic CHF
- Dyspnea or clinically significant hypotension (defined per investigator discretion)
- Symptomatic left ventricular dysfunction (NCI CTCAE v4.0 Grade 3 or 4) with a drop in LVEF consistent with cardiac failure
- Asymptomatic decline in LVEF as per cardiac algorithm (see Figure 4)

Details of discontinuation due to toxicity are given in Section 5.1.1.

Patients who discontinue all study drugs will be asked to return to the clinic for a post-treatment safety follow-up visit **28 days after the last dose** (see Appendix 1 and Section 4.5) and will undergo follow-up assessments until predefined end of the study (see Appendix 1 for details). The primary reason for each study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug will not be replaced.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate **this study** at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right **to close a site** at any time. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 Toxicity Management Guidelines

The NCI CTCAE v4.0 will be used to grade toxicity.

Herceptin SC, Perjeta IV, and docetaxel will be given as specified in Section 4.3.2 and Table 1.

Before starting a new treatment cycle, toxicity must have resolved as specified in Sections 5.1.1.1, 5.1.1.2, 5.1.1.3, and 5.1.1.4.

Herceptin SC, Perjeta IV, and docetaxel IV administration may be delayed to assess or treat adverse events such as cardiac adverse events, myelosuppression, or other events. No dose reduction will be allowed for Herceptin SC or Perjeta IV. If any of the individual study medications must be delayed for **≥1 day**, all three agents (Herceptin SC, Perjeta IV, and docetaxel IV) should be delayed for the same timeframe.

5.1.1.1 Cardiac Safety

All patients must have a baseline LVEF ≥50%. LVEF will be monitored regularly according to the Schedule of Assessments (see Appendix 1). If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement should be performed.

Symptomatic Left Ventricular Systolic Dysfunction will be reported on the basis of NCI CTCAE criteria v4.0 and NYHA classification (see Appendix 4 for details of the NYHA classification and left ventricular systolic dysfunction NCI CTCAE v4.0 grading).

Herceptin SC, Perjeta IV, and docetaxel will be discontinued in any patient who develops clinical signs and symptoms suggesting symptomatic CHF with the diagnosis confirmed by a suggestive chest X-ray and a drop in LVEF by ECHO or MUGA. CHF should be treated and monitored according to standard medical practice.

Asymptomatic LVEF Decline (LVEF assessment scheduled in Appendix 1).

There are two parts.

Part 1: Patient management according to algorithm shown in Figure 4.

To ensure the safety of patients in the trial, Herceptin SC and Perjeta IV must be withheld in all patients for whom:

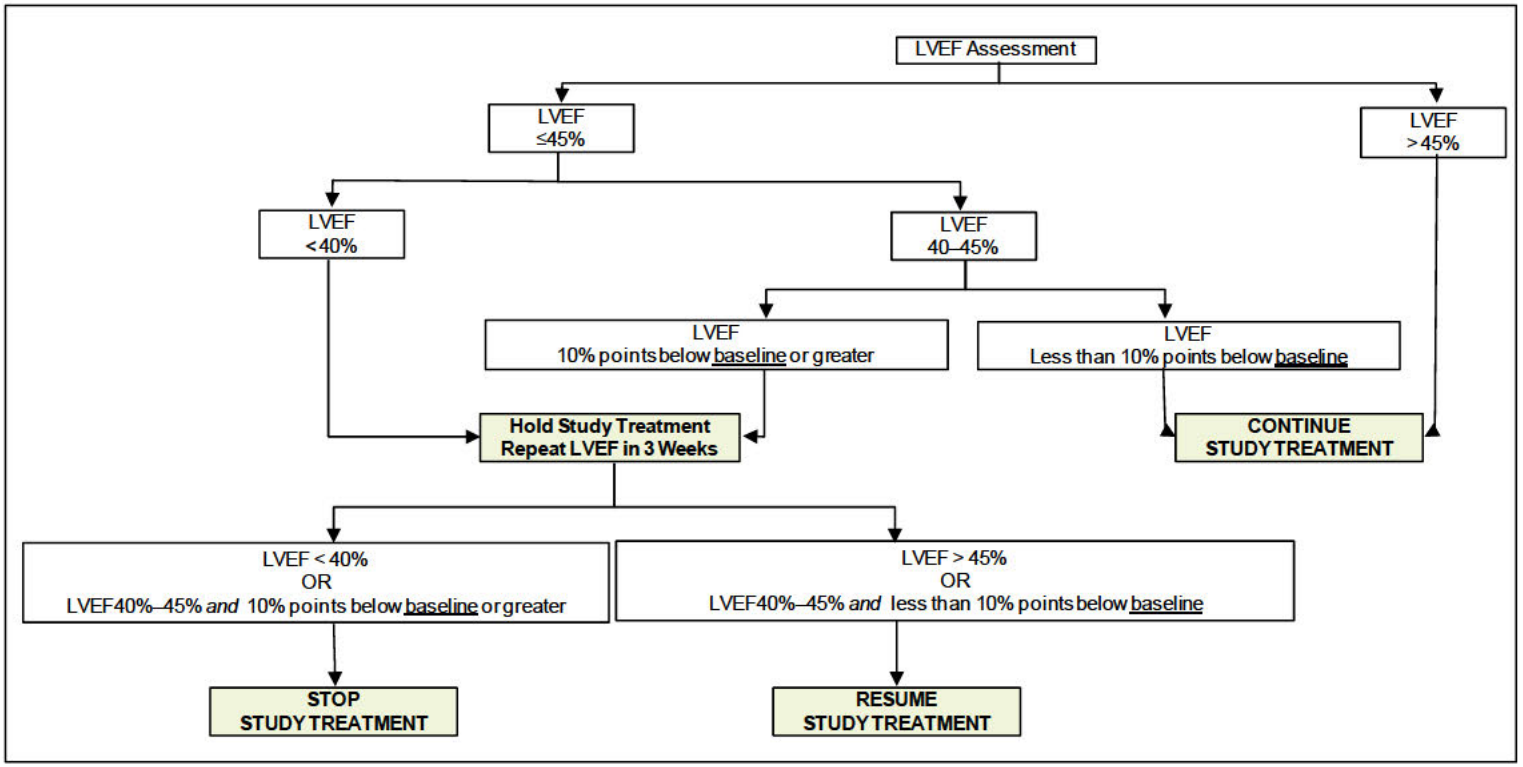
- **A decline of LVEF to <40%** is documented. If this value is confirmed within 3 weeks of the first assessment with use of the same assessment method, study drug must be discontinued.
- **LVEF decline to values 40–45% and ≥10% points** below baseline, the decision to stop or continue study treatment is based on the algorithm shown in Figure 4

Part 2: Reporting in eCRF as per NCI CTCAE criteria v4.0 (see Appendix 4).

The intensity of asymptomatic LVEF decline described above will be reported on the basis of NCI CTCAE criteria v4.0 (“Ejection fraction decreased“).

The incidence of CHF will also be recorded throughout the study.

Figure 4 Asymptomatic Decline in Left Ventricular Ejection Fraction: Algorithm for Continuation and Discontinuation of Perjeta and Herceptin Based on Left Ventricular Ejection Fraction Assessments



LVEF = left ventricular ejection fraction.

5.1.1.2 Administration-Related Reactions, Hypersensitivity Reactions, and Local-Site Reactions

Administration of monoclonal antibodies, including Herceptin SC and Perjeta IV, may cause ARRs. These include all adverse events leading to a systemic reaction following Herceptin SC, Perjeta IV, or docetaxel IV administration and which are considered related to the administration. Typically, adverse events such as chills and/or fever, dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, skin rashes, headache, nausea, or vomiting have been observed.

ARRs should be distinguished from local-site reactions, occurring after Herceptin SC injection or at the IV injection site of Perjeta or docetaxel. Local-site reactions are captured separately from ARRs.

ARRs may be clinically difficult to distinguish from hypersensitivity reactions.

Patients with extensive metastatic pulmonary disease involvement (e.g., lymphangitis, multiple metastases, and recurrent pleural effusions) and patients with preexisting pulmonary compromise who are treated with Herceptin may be at increased risk of severe or serious ARRs. Therefore, careful consideration must be made before enrolling patients with chronic pulmonary disease into the study.

Study treatment will be administered by staff trained to monitor for and respond to medical emergencies in a setting with emergency equipment.

Patients who experience the following events will be **discontinued** from the study treatment that is considered responsible for the event:

- Grade 4 hypersensitivity reaction,
- Acute respiratory distress syndrome (ARDS), or
- Bronchospasm

Patients who experience ARRs may be managed by:

- Slowing or stopping the Perjeta infusion for a Perjeta-related ARR
- Supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids as appropriate at the investigator's discretion

Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent Herceptin SC or Perjeta infusions at the investigator's discretion.

In order to be able to calculate time to onset of such reactions, the occurrence of adverse events has to be documented with the **date** and **time** of the **onset** and duration of the event (i.e., **resolution** of the event).

If a subject experiences an ARR, the diagnosis should be used for the primary adverse event term (e.g., “infusion-related reaction,” “injection-site reaction,” or “anaphylactic reaction”).

The individual sign(s) and symptom(s) of the reaction, separated by local or systemic ones, should then be captured on forms dedicated for systemic injection reactions, systemic infusion reactions, local infusion-site reactions, and local injection-site reactions (see Section 5.3.5.1).

If a patient experiences a local and a systemic reaction following administration of a single dose of study drug, then two separate adverse events will need to be recorded.

Patients will be monitored until complete resolution of signs and symptoms of any systemic reactions.

5.1.1.3 Incomplete Dose or Dose Delay

Perjeta IV

Incomplete Loading Dose

In case the whole loading dose of Perjeta IV cannot be administered because of an ARR or other reason, the following guidelines apply:

- The patient should receive at **least 50% of the loading dose** in the first week. Therefore, if the patient receives $<$50% of the Cycle 1 dose, the patient should receive the remainder of the dose before Day 22, preferably within the first week. Thereafter, the patient should receive the usual maintenance dose 3 weeks after the first interrupted dose, as routinely scheduled. For example, if a patient received only 50% of the scheduled loading dose (i.e., only 420 mg instead of 840 mg of Perjeta IV), the patient should receive the remaining dose (420 mg of Perjeta IV), preferably in the first week, and then regular maintenance doses (420 mg of Perjeta IV) on Day 22, as routinely scheduled.
- If the patient receives **between 50% and 75% of** the loading dose, the patient should receive the remainder before Day 22, preferably within the first 2 weeks of Cycle 1. For example, if a patient received approximately only 60% of the scheduled loading dose, the patient should receive the remaining 40% within 2 weeks after the interrupted loading dose. Thereafter, the patient should receive the regular maintenance doses on Day 22, as routinely scheduled.
- If the patient receives $\geq$**75% of the loading dose**, additional loading is probably not necessary. However, the remainder of the loading dose may be given at the investigator's discretion. In such a case, the remainder may be given at any time before the next scheduled dose, or the patient may be given an additional loading dose on Day 22. If, after receiving an incomplete loading dose on Day 1, the patient cannot attend the site until Day 22, the patient should receive a second loading dose on Day 22. However, every effort should be made to give the remainder of the dose prior to Day 22.

Dose Delay

If a **dose is delayed** (i.e., the time between two sequential infusions is <**6 weeks**), the 420 mg dose of Perjeta IV should be administered as soon as possible. Do not wait until the next planned dose.

If a dose is missed (i.e., the time between two sequential infusions is ≥**6 weeks**), a reloading dose of Perjeta IV (840 mg) should be given as described in the product labeling. If reloading is required for a given cycle, the three study therapies should be given on the same schedule as Cycle 1. Subsequent maintenance Perjeta IV doses of 420 mg will then be given every 3 weeks, starting 3 weeks later.

Herceptin SC

In the event a dose of Herceptin SC is incomplete, that dose will not be completed. Patients will receive the next scheduled dose per the Schedule of Assessments in Appendix 1.

No dose adjustment is needed in case of delayed administration of Herceptin SC as a fixed dose of Herceptin SC is used in this study.

5.1.1.4 Docetaxel Dose Modification for Toxicity

Docetaxel should be administered only under the supervision of a physician who is experienced in the use of cytotoxic cancer agents.

Significant hypersensitivity reactions can occur in patients who receive docetaxel, even after they receive adequate premedication. In the case of severe hypersensitivity reactions, docetaxel infusion should be discontinued immediately, symptomatic therapy should be initiated, and the patient should not be re-challenged with docetaxel. Localized skin erythema of the palms of the hands and soles of the feet with edema followed by desquamation has been observed with docetaxel.

Patients with severe fluid retention, such as pleural effusion, pericardial effusion, and ascites, should be monitored closely.

Dose reduction should occur in the case of development of severe peripheral neurotoxicity with docetaxel.

Table 2 Docetaxel Dose Adjustments

Docetaxel Dose	When
75 mg/m^2	Starting dose Administer **only** if neutrophil count is $>$1500 cells/mm^3
100 mg/m^2	At the discretion of the treating physician, after at least 1 cycle of 75 mg/m^2 without any of the following toxicities: • Febrile neutropenia • Grade 4 neutropenia for $>$5 days • ANC $<$100/μL for more than 1 day • Other non-hematological toxicities of Grade $>$2 (NCI CTCAE, v4.0)
55 mg/m^2 (or 75 mg/m^2 if dose previously increased to 100 mg/m^2)	25% reduced dose in case of any of the following toxicities: • Febrile neutropenia or neutrophils $<$500 cells/mm^3 for more than 1 week (after fully recovering to a neutrophil count $\geq$1500 cells/mm^3) • Platelet count $<$100,000 cells/mm^3 (after recovering to a platelet count $\geq$100,000 cells/mm^3) • Severe or cumulative cutaneous reactions
Permanently discontinue docetaxel	After any of the following toxicities: • Severe hypersensitivity reactions • Peripheral neuropathy $>$Grade 3 • Severe or cumulative cutaneous reactions that continue at a dose of 55 mg/m^2 without recovery • Febrile neutropenia or neutrophils $<$500 cells/mm^3 without recovery • Platelet $<$100,000 cells/mm^3 without recovery • Total bilirubin $>$ULN without recovery • Serum transaminase (AST/ALT) levels $>1.5\times$ ULN concurrent with serum alkaline phosphatase levels $>2.5\times$ ULN without recovery

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

Heart failure has been observed in patients who received docetaxel in combination with Herceptin. Cardiac function should be carefully monitored in patients who receive Herceptin with docetaxel. Details on monitoring of cardiac toxicity are given in Section 5.1.1.1).

Limited, non-comparative data from Phase I/II studies suggest that the combination of Perjeta and docetaxel may also result in myelosuppression. Given these data, it is expected that patients in this trial could experience hematologic adverse events while receiving treatment. For this reason, all patients will be monitored for hematologic events, and dose reductions of docetaxel with or without growth factor (e.g., G-CSF) support will be allowed in this protocol.

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60/Protocol BO29159, Version 2

Warning and precautions for docetaxel IV: The IV chemotherapy drug docetaxel contains 50 vol % ethanol (alcohol) (i.e., up to 0.395 g [0.5 mL] per vial), equivalent to 10 mL of beer or 4 mL wine per vial (Taxotere EPAR product information update 16 Jun 2014; available at www.ema.europa.eu/ema).

- Harmful for those suffering from alcoholism
- To be taken into account in pregnant or breastfeeding women, children, and high-risk groups such as patients with liver disease, or epilepsy
- The amount of alcohol in this medicinal product may alter the effects of other medicinal products.
- The amount of alcohol in this medicinal product may impair the patient's ability to drive or use machines.

For further information, refer to the local prescribing information for docetaxel.

5.1.2 Warning and Precautions for Herceptin SC

Herceptin SC therapy should be initiated only under supervision of a physician who is experienced in the treatment of patients with cancer.

Serious adverse reactions, including cardiac dysfunctions, ARRs, hypersensitivity, allergic-like reactions, and pulmonary events, have been observed in patients receiving Herceptin therapy. For some patients, symptoms progressively worsened and led to further pulmonary complications. Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported.

Fatalities have occurred within hours and up to 1 week following Herceptin IV administration. On very rare occasions, patients have experienced the onset of administration-related symptoms or pulmonary symptoms more than 6 hours after the start of the Herceptin administration. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur. Patients who have dyspnea at rest due to comorbidities may be at increased risk of a fatal ARR.

5.1.2.1 Administration-Related Reactions, Allergic-Like Reactions, and Hypersensitivity

Serious adverse reactions to Herceptin IV that have been reported infrequently include dyspnea, hypotension, wheezing, bronchospasm, asthma, tachycardia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, and angioedema. Although such events were not reported in the clinical trial with Herceptin SC, caution should be exercised as these events have been associated with the IV formulation.

These reactions were usually associated with the first administration of Herceptin and generally occurred during or immediately following administration.

Patients should be observed for administration-related reactions for 6 hours after the first injection of Herceptin SC and for 2 hours after subsequent injections.

In the pivotal study BO22227, there was a higher rate of Herceptin SC injection-site reactions compared with the Herceptin IV infusion (11.1% in Herceptin SC vs. 0.3% in Herceptin IV). With few exceptions, all of these events were of Grade 1 intensity.

ARRs were more commonly observed in patients who received Herceptin SC (47.8% in Herceptin SC vs. 37.2% in Herceptin IV). Erythema and cough were the primary adverse events responsible for the observed difference. The large majority of events (97%) were of Grade 1 or 2 intensity.

Serious reactions to Herceptin IV have been treated successfully with supportive therapy, such as oxygen, β-agonists, and corticosteroids.

5.1.2.2 Pulmonary Events

Caution is recommended with use of the Herceptin SC formulation as severe pulmonary events have been reported with the use of the Herceptin IV formulation in the post-marketing setting. These events have occasionally been fatal. They may occur as part of an ARR or with delayed onset. In addition, cases of interstitial lung disease, including lung infiltrates, ARDS, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema, and respiratory insufficiency, have been reported with Herceptin IV. These have been most common with the first infusion, and their severity has decreased with subsequent infusions. Serious reactions have been treated successfully with supportive therapy, such as oxygen, β-agonists, and corticosteroids. ARDS has been reported with a fatal outcome.

5.1.2.3 Cardiac Dysfunction

Heart failure (NYHA Class II–IV) has been observed in patients who have received Herceptin therapy alone or in combination with docetaxel following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. This may be moderate to severe and has been associated with death.

Risk factors for Herceptin-associated cardiac dysfunction include increased age, concomitant administration with anthracyclines, and declining LVEF while on Herceptin treatment. If symptomatic cardiac failure develops during Herceptin therapy, it should be treated with the standard medications for this purpose.

Because the half-life of Herceptin is approximately 28–38 days, Herceptin may persist in the circulation for up to 27 weeks after Herceptin treatment is stopped. Patients who receive anthracyclines after stopping Herceptin may possibly be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Most patients who developed heart failure in the Phase III trials of Herceptin in MBC improved with standard medical treatment. This treatment included diuretics, cardiac glycosides, and/or angiotensin-converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued on weekly therapy with Herceptin without experiencing additional clinical cardiac events.

5.1.3 Warning and Precautions for Perjeta

Perjeta therapy should be initiated only under supervision of a physician who is experienced in the treatment of patients with cancer.

5.1.3.1 Risk of Hypersensitivity Reactions, Including Anaphylaxis and Administration-Related Symptoms

ARRs typically occur during or shortly after the administration of monoclonal antibodies but may also show a delayed onset. The true relation of an event to administration of study treatment is therefore difficult to ascertain, particularly when treatment regimens involve combination therapy.

In general, antibody administration-related adverse events are more frequent and severe with the first infusion and decrease in number and severity over time. The majority of adverse events resolve fully.

Perjeta will be administered by staff trained to monitor for and respond to medical emergencies in a setting with emergency equipment. Patients will be monitored during each Perjeta infusion and for 30–60 minutes (60 minutes for the initial administration) following the completion of the infusion for any adverse effects. If administration-related symptoms occur, patients will be monitored until complete resolution of signs and symptoms. Patients who experience administration-related symptoms may subsequently be premedicated with acetaminophen, diphenhydramine, or meperidine.

Infusion of Perjeta should be stopped in patients who develop dyspnea or clinically significant hypotension (defined per investigator discretion). Patients who experience a Grade 3 or 4 hypersensitivity reaction or ARDS should not receive additional Perjeta.

Refer to the Perjeta Investigator's Brochure for the most recent data related to the risk of hypersensitivity reactions.

5.1.3.2 Risk of Cardiac Dysfunction

Like Herceptin, Perjeta is directed at the HER2 receptor and may be associated with a risk of cardiac dysfunction.

Patients with significant cardiac disease or baseline LVEF $<$50% are not eligible for this study.

In the pivotal Phase III study CLEOPATRA in patients with MBC, Perjeta in combination with Herceptin and docetaxel was not associated with an increase in the incidence of symptomatic LVSD (CHF) or decreases in LVEF compared with placebo in combination with Herceptin and docetaxel. However, patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF.

In the neoadjuvant setting (NEOSPHERE), the incidence of LVSD was higher in patients treated with Perjeta than in patients treated with Herceptin and docetaxel. An increased incidence of LVEF decline was observed in patients treated with Perjeta in combination with Herceptin and docetaxel; LVEF recovered to $\geq 50\%$ in all patients during the treatment period.

Perjeta has not been studied in patients with a pretreatment LVEF value of $< 50\%$, a prior history of CHF, decreases in LVEF to $< 50\%$ during prior Herceptin adjuvant therapy, conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment, or a cumulative prior anthracycline exposure to > 360 mg/m^2 of doxorubicin or its equivalent.

Risk factors for Perjeta-associated cardiac dysfunction should be carefully weighed against the potential benefit in patients who have received prior anthracyclines. During the screening/baseline period, complete medical history information will be collected from all patients to explore possible risk factors for treatment-associated CHF.

Monitoring of LVEF is required while patients are receiving study treatment.
If symptomatic left ventricular dysfunction develops (NCI CTCAE v4.0 Grade 3 or 4) with a drop in LVEF consistent with cardiac failure, the patient must discontinue study treatment. Left ventricular dysfunction, whether symptomatic or not, should be treated and followed according to standard medical practice.

The Perjeta Investigator's Brochure should be referred to for most recent data relating to risk of cardiac dysfunction.

5.1.3.3 Risk of EGFR-Related Toxicities

Although Perjeta targets HER2 because of its role in heterodimerization with other members of the HER family (e.g., EGFR), it may cause toxicities associated with the use of EGFR TK inhibitors. In the 7-week IV and 26-week toxicity studies in cynomolgus monkeys, there were treatment-related increases in the incidence of diarrhea.

Diarrhea has been observed in patients who are treated with Perjeta in Phase II single-agent studies and in combination therapy studies. For patients who experience diarrhea, early intervention with loperamide should be considered.

Rash has also been observed with EGFR TK inhibitors.

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The Perjeta Investigator's Brochure should be referred to for most recent data relating to the risk of EGFR-related toxicities.

5.1.4 Pregnancy

ICH M3 Guidance requires precautions to be taken to minimize risk to fetus or embryo when including WOCBP. This includes the use of highly effective contraceptive measures, excluding pregnancy at baseline (serum test), continued pregnancy monitoring, and continued pregnancy testing up to 7 months following last dose of study drug (follow-up period based on pharmacokinetic considerations).

Reproductive toxicity was identified during preclinical studies; both Herceptin and Perjeta administered to pregnant cynomolgus monkeys during organogenesis led to oligohydramnios, delayed renal development, and embryo-fetal deaths. There are no clinical studies of Herceptin or Perjeta in pregnant women. IgGs are known to cross the placental barrier. Therefore, neither Perjeta nor Herceptin should be used during pregnancy.

WOCBP (who have not undergone surgical sterilization) must agree to use a highly effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner.

Methods of birth control that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are considered **highly effective forms** of contraception. The following non-hormonal methods of contraception are acceptable:

- True abstinence when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal postovulation methods] and withdrawal are not acceptable methods of contraception.)
- Male sterilization (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomized male partner should be the sole partner.

Or two of the following effective forms of contraception:

- Placement of intrauterine device (IUD) or intrauterine system (IUS). Consideration should be given to the type of device being used as there are higher failure rates quoted for certain types (e.g., steel or copper wire). The risks (in terms of potential stimulation of hormone-responsive breast cancer by systemically absorbed hormones) and benefits (effective contraception) of hormone-releasing IUDs/IUSs should also be carefully considered for individual patients.
- Condom with spermicidal foam/gel/film/cream/suppository
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:

- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection.
- However, spermicides alone are ineffective at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

It should be noted that **two forms of effective contraception are required**. A double-barrier method is acceptable, which is defined as condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

Postmenopausal is defined as ≥ 12 months of amenorrhea (see details in Section 4.5.2).

On the basis of pharmacokinetic considerations, contraception must continue for the duration of study treatment and for **at least 7 months** after the last dose of study treatment.

It is not known whether Herceptin or Perjeta is excreted in human milk. As maternal IgG is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during Perjeta or Herceptin therapy and not to breastfeed for at least 7 months following the last dose of either monoclonal antibody.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events including serious adverse events and non-serious adverse events that are immediately reportable, performing of protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except for preexisting medical condition as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life-threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (for details see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, severe, life-threatening or fatal according to NCI CTCAE v4.0 criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

5.2.3 Non-Serious Adverse Events (Immediately Reportable to the Sponsor)

Non-serious adverse events that are immediately reportable are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

For this study, this applies for the following adverse events:

- CHF
- An asymptomatic decline in LVEF that requires treatment or that leads to discontinuation of study treatment
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug
- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

Note: In general, asymptomatic declines in LVEF should not be reported as adverse events since LVEF data are collected separately in the eCRF. Exceptions to this rule are as follows:

- An asymptomatic decline in LVEF to a value of 10 percentage points below baseline or lower and $<$50% must be reported as an adverse event
- An asymptomatic decline in LVEF that requires treatment or that leads to discontinuation of study treatment must be reported in an expedited manner with use of the Serious Adverse Event form and classifying the event as a Non-Serious Event that is Immediately Reportable

For reporting in eCRF: Both cases should be reported as "Ejection fraction decreased" and graded according to NCI CTCAE v4.0.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4, 5.5, and 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

For each local-site reactions and systemic ARR recorded on the corresponding dedicated eCRF, the **date** and **time of onset** and the **date and time of resolution** has to be recorded (see Sections 5.1.1.2 and 5.3.5.1).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events considered to be related to a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies).

After initiation of study drug, all adverse events will be reported until the post-treatment safety follow-up visit (i.e., approximately 28 days after the last dose of study drug).

Adverse events that are ongoing at the time of the post-treatment follow-up visit should be followed depending on the event type:

- All cardiac adverse events (regardless of seriousness or causality) and all serious adverse events (regardless of causality) should be followed until resolution/stabilization/death up to 1 year after the last dose or end of the study, whichever comes first.
- Non-cardiac, non-serious adverse events (regardless of causality) should be followed **only** until the post-treatment follow-up visit.

Only the following new adverse events that start after the post-treatment follow-up visit should be reported to the clinical database:

- Cardiac events (regardless of causality or seriousness) that start up to 2 years after the last dose should be reported. These events should be followed until resolution/stabilization/death up to 2 years after the start of the event or end of the study, whichever comes first.
- Herceptin SC and Perjeta IV-related serious adverse events should be reported at any time regardless of the start date. These events should be followed until resolution/stabilization/death up to 1 year after the start of the event.

After the end of the study, the investigator should report any serious adverse events that are believed to be related to study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. The guidelines in Table 3 will be used to assess ONLY the severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (version 4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must also be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must also be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or re-introduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

For patients who receive combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Administration-Related Reactions and Local Injection-Site Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion or injection should be captured as a diagnosis (e.g., “infusion-related reaction,” “injection-site reaction,” “anaphylactic reaction”) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as “systemic reaction.”

Associated signs and symptoms should be recorded on the dedicated Administration-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF with signs and symptoms also recorded separately on the dedicated Administration-Related Reaction eCRF (see Section 5.1.1.2).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than ARRs (see Section 5.3.5.1), a final diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and

symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by adverse event report based on the single diagnosis with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continually, without resolution, between patient evaluation timepoints. Such events should be recorded only once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium" as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should be recorded only once on the Adverse Event eCRF, (see Section 5.3.5.4 for details on recording persistent adverse events).

Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded on the eCRF.

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should be recorded only once on the Adverse Event eCRF, (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin).
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Serious Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of the underlying disease of metastatic breast cancer should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An internal monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, **only one** such event should be reported.

The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.

If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

During survival follow-up, deaths attributed to new progression of disease should be recorded only on the Study Completion/Early Discontinuation eCRF page.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study.

When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the determination of progression will be based on RECIST v1.1 (see Appendix 5). In rare cases, the determination of clinical progression will be based on symptomatic deterioration.

However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for respite care

- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not suffered an adverse event.
- Hospitalization due solely to progression of the underlying cancer

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.3.5.13 Adverse Events in Individuals Not Enrolled in the Study

If an adverse event inadvertently occurs in an individual not enrolled in the study (e.g., during administration of study drug), the Adverse Event Form provided to investigators should be completed and submitted to Roche or its designee, either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The investigator must report the following events to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events that are immediately reportable as defined in Section 5.2.3
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor within 24 hours after becoming aware of the information. New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB or IEC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Sponsor Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Sponsor Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk as well as Medical Monitor contact information will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events that are Immediately Reportable

For reports of serious adverse events and non-serious adverse events that are immediately reportable, investigators should record all case details that can be gathered within 24 hours on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Non-Serious Adverse Event that is Immediately Reportable CRF and fax cover sheet should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

As described in Section 5.1.4, female patients of childbearing potential are required to use one highly effective form of contraception or use two effective forms of contraception.

Female patients of childbearing potential will be instructed to immediately inform the investigator if she becomes pregnant during the study or within 7 months after study

treatment. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. A pregnancy report will automatically be generated and sent to the Sponsor's Safety Risk Management department. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drugs and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue **until** conclusion of the pregnancy. Additional information on any Herceptin SC or Perjeta IV-exposed pregnancy and infant will be requested by Roche Drug Safety at specific timepoints (i.e., at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS WITH ONGOING ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event as described in Section 5.3.1. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow-up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (see Section 5.3.1), if the event is believed to be related to study drug treatment.

The investigator should report these events directly to Roche or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Herceptin and Perjeta Investigator's Brochures

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness with allowance for upgrading by the Sponsor as needed.

5.8 REVIEW OF SAFETY BY AN INTERNAL MONITORING COMMITTEE

An IMC will be established for the study with Roche members who are independent from the BO29159 study team. The IMC membership will include representatives from

clinical science, safety science, and biostatistics. Specific policies on the operation of the IMC will be documented in an IMC Charter.

The IMC will meet on a regular basis over the course of the study and may also meet on an unscheduled basis if any unexpected safety concerns arise.

The details of the IMC will be provided in a separate charter document.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The cutoff for the final analysis will be **24 months** after the last patient is enrolled.

In addition to the final analysis, there will be an interim analysis approximately 6 months after recruitment of the last patient to determine overall safety and tolerability with emphasis on cardiac safety and efficacy. Given the objective of the study, the Sponsor may choose to adapt the timepoint of the interim analysis or to conduct additional interim analyses as appropriate (see Section 6.7).

Efficacy and safety populations will be identical in this study and include all enrolled patients who received at least one dose of any study drug.

6.1 DETERMINATION OF SAMPLE SIZE

The main objective of this safety study is the characterization of the safety profile and tolerability of Herceptin SC in combination with Perjeta IV and docetaxel based on an estimation of the incidence of adverse events. This is not a hypothesis testing study but an exploratory study with predefined precision of estimates for key safety parameters for sample size determination; there are no formal statistical hypothesis tests to be performed, and there will be no adjustments for multiplicity of endpoints or within-subgroups comparisons.

The proposed sample size to be enrolled in this study is 400 patients with the following rationale:

- The width of the 95% Pearson Clopper CI of the incidence of Grade ≥3 adverse events is reasonably small (71.8%, 80.3%) with 400 treated patients based on the observed incidence of Grade ≥3 adverse events of 76.2% for patients who were treated with Perjeta in combination with Herceptin IV in the TOC4129g/WO20698 study.
- Furthermore, with 400 treated patients on the observed incidence of cardiac events Grade ≥3 of 1.7% reported in the TOC4129g/WO20698 study, the width of the 95% Pearson Clopper CI of the incidence of Grade ≥3 cardiac adverse events is reasonably small (0.7%, 3.6%).

6.2 SUMMARIES OF CONDUCT OF STUDY

The major protocol deviations will be summarized.

Enrollment, patient disposition, study treatment administration, and discontinuations from the study will be summarized. The incidence of treatment discontinuation for reasons other than disease progression will be tabulated.

The duration of follow-up will be summarized by summary statistics of mean, median, range, standard deviation, and 25th–75th quartiles.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

There is only one treatment group in this study.

Baseline and disease characteristics, such as demographics, medical history, etc., will be summarized by descriptive statistics (frequency tables for categorical variables and mean, median, range, standard deviation, and 25th–75th quartiles for the continual variables). These characteristics will be summarized for all patients who are enrolled and treated in the study.

6.4 EFFICACY ANALYSES

The efficacy analyses will include all enrolled patients who received at least one dose of any study drug.

Efficacy outcome measures for this study are to evaluate Herceptin SC in combination with Perjeta plus docetaxel with respect to PFS, OS, and ORR.

PFS based on investigator assessment is defined as the time from first dose of study drug administration to the first radiographically documented progression of disease, as determined by the investigator using current RECIST v1.1 (see Appendix 5; Eisenhauer et al. 2009) or death from any cause, whichever occurs first. Carcinomatous meningitis diagnosed by cytologic evaluation of cerebral spinal fluid will also define PD. Medical photography will also be allowed to monitor chest wall recurrences of subcutaneous lesions.

Overall survival: OS is defined as the time from the date of first dose of study drug administration to date of death from any cause.

Objective response: Objective response is defined as a CR or PR determined by the investigator using current RECIST v1.1 (see Appendix 5; Eisenhauer et al. 2009) on two consecutive occasions ≥4 weeks apart. Patients with disease localized only to the bone will not be included in the analysis of objective response.

6.5 SAFETY ANALYSES

The safety analyses will include all enrolled patients who received at least one dose of any study drug.

The safety variables are all adverse events, adverse events Grade ≥3 according to the NCI CTCAE v4.0, adverse events leading to treatment interruption and discontinuation, serious adverse events, causes of deaths, incidence of CHF, incidence of cardiac adverse events Grade ≥3, LVEF decline (≥10% points from baseline to below 50%), premature discontinuation from study and treatment, and laboratory parameters. The primary interest in this study will be to estimate the incidence of adverse events Grade ≥3 for the treatment of Herceptin SC in combination with Perjeta and docetaxel.

The analysis of adverse events will focus on treatment-emergent adverse events (i.e., adverse events that occur during or after the first administration of study drug). Non–treatment-emergent adverse events (i.e., those that occur during screening) will be listed only during the screening period. Only the serious adverse event related to a protocol-mandated procedure will be reported and all adverse events that occurred before Day 1 (first administration) would be reported in medical history.

The incidence, type, and severity of adverse events will be summarized according to the primary System Organ Class (SOC) and within each SOC, by MedDRA preferred term.

Adverse events Grade ≥3, adverse events leading to treatment modification and discontinuation, and serious adverse events will be analyzed in a similar way to all adverse events. Causes of deaths will also be summarized and listed.

LVEF as well as changes from baseline over time will be analyzed using descriptive statistics for continuous variable and presented graphically over time with associated 95% CI. The percentage of patients with an LVEF decline ≥10% points from baseline to below 50% will be summarized.

The number of patients who prematurely discontinue from study treatment with a corresponding reason for discontinuation will be summarized and listed.
The discontinuation from study will be also summarized and listed.

Descriptive statistics will be presented for cumulative study medication doses and duration of exposure.

Subgroup analysis of all grade adverse event variables will be performed for patients receiving at least one cycle of 100 mg/m^2 docetaxel.

The following subgroup analysis will be performed for LVEF decline of more than 10% points from baseline to below 50%, CHF, cardiac adverse events Grade ≥3:

- Other selected safety variables—race
- Known risk factors for development of cardiac related events—age, medical history of hypertension, prior treatment with anthracyclines, LVEF at baseline

The incidence and severity of ARR adverse events will be summarized. Time to onset of the first ARRs and time from onset to resolution of ARRs will also be summarized. In addition, the ARR analyses will also be performed for each treatment cycle.

Laboratory parameters, hematology, and serum biochemistry will be presented in shift tables of NCI CTCAE v4.0 grade at baseline versus worst grade during the treatment period. The summary of laboratory parameters will also be presented by means, standard deviation, minimum, and maximum. The selected laboratory parameters will be also graphically presented over time.

6.6 IMMUNOGENICITY ANALYSES

Immunogenicity analyses will be performed using the safety population. Incidence of baseline and post-baseline anti-Herceptin and anti-rHuPH20 antibody rates will be summarized. All patients with at least one anti-Herceptin and/or anti- rHuPh20 confirmed positive result will be listed. Calculation of mean Herceptin concentration by antibody status (positive/negative) at each antibody timepoint will be performed to assist in the assessment of antibody development. Subgroup analysis by antibody status will be performed for incidence of ARRs.

6.7 INTERIM ANALYSES

In addition to the final analysis, there will be an interim analysis approximately 6 months after recruitment of the last patient to determine overall safety and tolerability with special emphasis on cardiac safety and efficacy. Given the objective of the study, the Sponsor may choose to adapt the timepoint of the interim analysis or to conduct additional interim analyses if appropriate. The decision to adapt the timepoint of the interim analysis or to conduct an additional interim analysis will be documented in the Sponsor's trial master file prior to the conduct of the respective interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

There will also be an annual review of safety data by the IMC.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the EDC system and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the Roche policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB or IEC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; Appendix 2). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union/European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Form or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB or IEC submission. The final IRB or IEC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB or IEC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB or IEC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INDEPENDENT ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB or IEC by the Principal Investigator and reviewed and approved by the IRB or IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB or IEC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB or IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB or IEC. Investigators are also responsible for promptly informing the IRB or IEC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/IEC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB or IEC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB or IEC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB or IEC and governmental approval. In addition, at the end of the study the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB or IECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

An IxRS system will be used for enrollment of patients into the study.

A CRO will be used for data management (see Section 7.1).

Assessment of laboratory test results will be performed locally.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf.

The results of this study may be published or presented at congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Guidance from International Committee of Medical Journal Editors (ICMJE):

- Authors must meet ALL of the following authorship criteria: Substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data.
- Drafting or revising the abstract/manuscript for important intellectual content
- Final approval of the version to be published
- Accountability for all aspects of the work by ensuring that questions related to the accuracy of any part of the work are appropriately investigated and resolved
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB or IEC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1
Schedule of Assessments

	Screening	Baseline [a]	Treatment Period	Post-Treatment Follow-Up		
				Safety Follow-Up Visit Post-Treatment 28–35 Days after Last Dose of Study Treatment [c]	Follow-Up Every 12 Weeks ± 7 Days after Safety Follow-Up Visit	
	Day –28 to Day 1	Day –7 to Day 1	Each Treatment Cycle [b] (All Visits within ± 3 Days of Scheduled Treatment Day)		Until Disease Progression	After Disease Progression Until the End of the Study
Informed consent	x					
HER2 [d] status	If positive HER2 result not available					
Hormonal receptor status from primary tumor (and/or metastatic site, if primary tumor not available)	x					
Demographics and medical history [e]	x					
Menopausal status	x					
Tumor evaluation [f]	x		Every 9 weeks (± 3 days) from the first administration until disease progression			
Brain CT/MRI	x (if clinical suspicion of brain metastasis)		If clinically indicated			
Standard 12-lead ECG [g]	x		Every 3 cycles of monoclonal antibody (within 7 days **prior** to study treatment)	x		
LVEF [h] (ECHO or MUGA)	x			x	x	
Concomitant medications [i]	x	x	x	x	x	
Physical examination [j]		x	x	x		

Appendix 1
Schedule of Assessments (cont.)

	Screening	Baseline [a]	Treatment Period	Post-Treatment Follow-Up		
				Safety Follow-Up Visit Post-Treatment 28–35 Days after Last Dose of Study Treatment [c]	Follow-Up Every 12 Weeks ± 7 Days after Safety Follow-Up Visit	
	Day –28 to Day 1	Day –7 to Day 1	Each Treatment Cycle [b] (All Visits within ± 3 Days of Scheduled Treatment Day)		Until Disease Progression	After Disease Progression Until the End of the Study
Vital signs and blood pressure [j]		x	x	x	x	
Height		x				
Weight [j]		x	x	x		
Pregnancy test [k]		x	Every 3 cycles of monoclonal antibody prior to drug administration.	x	About 4 months and 7 mon hs after discontinuation of study treatment (during the closest follow-up visit)	
Hematology [l] and serum chemistry (local laboratory)		x	x	x		
INR and aPTT or PTT [l] (local lab)		x	x	x		
Blood sample for anti-trastuzumab and serum concentration analysis [m]		x	Pre-dose Cycle 2	x		
Blood sample for anti-rHuPH20 analysis [m]		x	Pre-dose Cycle 2	x		
ECOG Performance Status		x	Every 3 cycles of monoclonal antibody	x	x	
Serious adverse events/adverse events [n]	x	x	x	x	x (see Section 5.3.1)	x (see Section 5.3.1)
Record of post-study treatment cancer-related medical or surgical procedures [o]				x	x	x
Administration of study medication			x			

Appendix 1
Schedule of Assessments (cont.)

	Screening	Baseline [a]	Treatment Period	Post-Treatment Follow-Up		
				Safety Follow-Up Visit Post-Treatment 28–35 Days after Last Dose of Study Treatment [c]	Follow-Up Every 12 Weeks ± 7 Days after Safety Follow-Up Visit	
	Day –28 to Day 1	Day –7 to Day 1	Each Treatment Cycle [b] (All Visits within ± 3 Days of Scheduled Treatment Day)		Until Disease Progression	After Disease Progression Until the End of the Study
Administration-related reactions during infusion and observation period			x			
Survival [p]					x	x

ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor 2; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition; rHuPH20 = recombinant human hyaluronidase.

[a] Baseline/Screening assessments are allowable on Day 1 of first treatment cycle before dose as long as the results are available prior to first dose of study drug administration.

[b] Cycle = 3 weeks for monoclonal antibodies.

[c] At the post-treatment safety follow-up visit, all the assessments and sample collection has to be done before the start of any subsequent line of treatment.

[d] Demonstrated evidence of HER2-positive status from previous testing is acceptable. Otherwise HER2-positive status on fixed tissue blocks from the primary tumor (and/or metastatic site, if primary tumor not available) to be assessed locally by immunohistochemistry and/or in situ hybridization according to institutional criteria.

[e] Complete medical history (clinically significant diseases, surgeries, cancer history, etc.) and demographics (i.e., age, sex, race, and self-reported ethnicity, if applicable) and all medications taken within 28 days prior to the first dose administration (Day 1).

[f] A CT or MRI of the chest, abdomen, and pelvis and (if indicated) isotope bone scan (evaluation according to RECIST v1.1 criteria) should be performed at screening and as clinically indicated. Scans at screening should not be older than 28 days prior to **first study medication administration**. To be performed post-study treatment only if disease progression has not yet been established. Note: Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. Always schedule tumor assessments every 9 weeks ± 3 days from the date of first drug administration. If a tumor assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule of every 9 weeks from the date of first dose of study drug administration. All patients should have a minimum of a **chest** and **abdominal CT scan**. PET scans will not be considered for assessments of efficacy at any ime during the study (except as specified for bone scans in the absence of radioactive isotopes).

[g] ECG will be performed at screening (within 6 weeks prior to first dose of study drug) and **every three cycles** of monoclonal antibody therapy during the treatment period, at the time of LVEF measurement. ECGs should be performed within 7 days prior to administration of study drug.

Appendix 1
Schedule of Assessments (cont.)

[h] LVEF ≥ 50% at screening period to be determined by either ECHO or MUGA scan (with ECHO as the preferred method). The **same** method of LVEF assessment (ECHO or MUGA) must be used for the same patient throughout the study and, to the extent possible, be obtained at the same institution. All pre-study LVEF values during and following Herceptin adjuvant treatment for patients who received such adjuvant herapy prior to first dose of study drug administration into he study will be collected. LVEF assessment (ECHO or MUGA) during the screening period within 6 weeks prior to first dose of study drug does not need to be repeated. To be performed **every three cycles within 7 days of monoclonal antibody therapy** during the treatment period and at safety follow-up visit if previous result is older than 9 weeks. If an LVEF assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule from the date of first dose of study drug administration. After post-treatment follow-up visit, LVEF assessment will be done **every 6 months** in the first year and then **annually for up to 2 years** after post-treatment safety follow-up visit at 6, 12, and 24 months. Patients for whom study treatment was permanently discontinued because of a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 3 months until the LVEF values return to ≥ 50% or until 1 year after post-treatment safety follow-up visit at 3, 6, 9, 12, and 24 months, whichever occurs first. Thereafter, LVEF assessments will be performed annually for up to 2 years after post-treatment safety follow-up visit.

[i] Concomitant medication will be recorded at baseline and on an ongoing basis until disease progression or end of the study, whichever occurs first.

[j] Physical examination, including vital signs, will be performed prior to first dose of study drug administration with particular care taken with regard to cardiovascular signs and symptoms (elevated jugular venous pressure, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.). A physical examination must be performed within 7 days prior to baseline. Vital signs will be assessed **before** treatment on Day 1 of every treatment cycle (Perjeta, Herceptin, and docetaxel) with blood pressure, pulse rate, and body temperature recorded **again after** administration during the observation period **of each** study medica ion.

[k] All women of childbearing potential (premenopausal women and for women < 12 months after the onset of menopause, unless hey have undergone surgical sterilization) will have a serum pregnancy test at a local laboratory within 7 days prior to the first administration of study medication. For all other women, documentation must be present in medical history confirming that he patient is not of childbearing potential. Urine pregnancy tests will be repeated during the treatment period within 7 days prior to every third treatment cycle starting at Cycle 3 (and as clinically indicated), as well as at the post-treatment safety follow-up visit and 4 and 7 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG evaluation at the local laboratory. Pregnancy test results must be available prior to the next scheduled study treatment. Women who have undergone surgical sterilization or are postmenopausal are exempt from pregnancy assessments.

[l] Assessment must be performed wi h results available within 3 days prior to the administration of study medication. Hematology will include hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and other cells). Serum chemistry will include sodium, potassium, calcium, chloride, magnesium, BUN (urea), total protein, albumin, alkaline phosphatase, ALT, AST, gamma-glutamyl transferase, LDH, total bilirubin, creatinine, blood glucose, and calculated creatinine clearance at baseline. All patients will have INR and aPTT or PTT testing at baseline. Tests will be repeated at each treatment cycle in all patients receiving therapeutic doses of anticoagulants. Assessment of coagulation must be performed within 3 days (with results available) prior to the administration of study medication.

[m] Samples for anti-Herceptin antibody and serum concentration and anti-rHuPh20 antibody are collected at baseline, prior to dosing on Day 1 of Cycle 2 and prior to any new treatment at the post-treatment safety follow-up 28–35 days after the last dose of Herceptin SC.

[n] After informed consent, but prior to initiation of study medications, only serious adverse events considered to be related to a protocol-mandated intervention will be collected. Adverse events to be monitored continually during the treatment period. See the details of adverse events reporting period Section 5.3.1 .

[o] Collect post-study treatment cancer-related medical or surgical procedures and therapies and survival information every 12 weeks after the treatment discontinuation visit during the post-treatment follow-up period until death, loss to follow-up, withdrawal of consent, or study termination by Roche.

[p] Survival status will be recorded every 12 weeks after he post-treatment safety follow-up 28–35 days after last dose of study treatment until the end of the study.

Appendix 2
ICH Guidelines for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2a

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any adverse event that at any dose fulfills at least one of the following criteria:

- Is fatal (results in death) (NOTE: death is an outcome, not an event)
- Is life-threatening (NOTE: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that could hypothetically have caused a death had it been more severe.)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the Sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

An unexpected adverse event is the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For serious adverse events, possible causes of the event **are** indicated by selecting one or more options. (Check all that apply.)

- Preexisting/underlying disease—specify
- Study treatment—specify the drug(s) related to the event
- Other treatment (concomitant or previous)—specify
- Protocol-related procedure
- Other (e.g., accident, new or intercurrent illness)—specify

Appendix 2
ICH Guidelines for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2a (cont.)

The term severe is a measure of intensity; thus, a severe adverse event is not necessarily serious. For example, nausea of several hours' duration may be rated as severe but may not be clinically serious.

Such preliminary reports will be followed by detailed descriptions later, which will include copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the adverse events page of the eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the IRB or IEC of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

SPONSOR LOCAL COUNTRY CONTACT for serious adverse events: Local Monitor.

SPONSOR HEADQUARTERS CONTACT for serious adverse events and other medical emergencies: Contact information for the Contract Research Organization responsible for drug safety will be provided separately.

24-HOUR MEDICAL COVERAGE: Identification of a contact for 24-Hour Medical Coverage is mandatory to be compliant with worldwide Regulatory Agencies and to ensure the safety of study patients.

An Emergency Medical Call Center Help Desk will access the Sponsor Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with the Sponsor medical contact for this study and track all calls. The Emergency Medical Call Center Help Desk will be manned 24 hours, 7 days a week. Toll-free numbers will be distributed to all investigators participating in this clinical trial. The Help Desk will be used for medical emergencies outside regular business hours or when the regular International Medical Leader cannot be reached.

See the Protocol Administrative and Contact Information & List of Investigators form for details of administrative, contact information, and Emergency Medical Call Center Help Desk toll-free numbers. This information will be provided separately.

Appendix 3
Eastern Cooperative Oncology Group Performance Status

Grade	Scale
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, i.e., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 4
New York Heart Association Classification and Left Ventricular Systolic Dysfunction National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 Grading

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or angina pain.
Class II	Patients with cardiac disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Weatherall DJ, Ledingham JGG, editors. Oxford Textbook of Medicine. Third Edition. New York: Oxford University Press, 1996.

NCI CTCAE v4.0 Grading

Cardiac disorders					
	Grade				
Adverse Event	1	2	3	4	5
Left ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death
Definition: A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations mayinclude dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.					
Heart failure	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.					

Appendix 4
New York Heart Association Classification and Left Ventricular Systolic Dysfunction National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 Grading (cont.)

Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.					

Common Terminology Criteria for Adverse Events. Version 4.0. Published May 28, 2009 (v4.03: 14 June 2010). US Department of Health and Human Services, National Institutes of Health, National Cancer Institute (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE-4.03-2010-06-14-QuickReference-5x7.pdf).

Appendix 5
Tumor Assessments (Response Evaluation Criteria in Solid Tumors) Version 1.1

1. Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot accurately be measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions: All other lesions including small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with P10 to $<$ 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Appendix 5
Tumor Assessments (Response Evaluation Criteria in Solid Tumors)
Version 1.1 (cont.)

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

2. Methods of measurements

Measurement of lesions

- All measurements should be recorded in metric notation with use of calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks (28 days) before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

- **Clinical lesions**: Clinical lesions will only be considered measurable when they are superficial and $\geq$10 mm diameter as assessed with use of calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested. When lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- **Chest X-ray**: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **CT/MRI**: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is

5 mm or less. As is described in "Specification for standard anatomical radiological imaging" (article Eisenhauer 2009, Appendix II), when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

- **Ultrasound**: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- **Endoscopy, laparoscopy**: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- **Tumor markers**: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease-specific basis.
- **Cytology/histology**: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and PD.

3. Tumor response evaluation

Assessment of overall tumor burden and measurable disease:

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above). In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Appendix 5
Tumor Assessments (Response Evaluation Criteria in Solid Tumors)
Version 1.1 (cont.)

Baseline documentation of 'target' and 'non-target' lesions:

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions, respectively, will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition, should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Appendix 5
Tumor Assessments (Response Evaluation Criteria in Solid Tumors)
Version 1.1 (cont.)

Response criteria

Evaluation of **target lesions**:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to $<$10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest in the study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while in the study.

Evaluation of **non-target lesions:**

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size ($<$10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression.)

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation.

The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR

is needed to deem either one the "best overall response." This is described further below.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Source: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

PROTOCOL

TITLE:	**A PHASE III PROSPECTIVE, TWO-COHORT NON-RANDOMIZED, MULTICENTER, MULTINATIONAL, OPEN-LABEL STUDY TO ASSESS THE SAFETY OF ASSISTED- AND SELF-ADMINISTERED SUBCUTANEOUS TRASTUZUMAB AS THERAPY IN PATIENTS WITH OPERABLE HER2-POSITIVE EARLY BREAST CANCER [SafeHer Study]**
PROTOCOL NUMBER:	MO28048
VERSION NUMBER:	4
EUDRACT NUMBER:	2011-005328-17
IND NUMBER:	Not applicable
TEST PRODUCT:	Trastuzumab SC (RO 45-2317)
MEDICAL MONITOR:	[redacted], Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 30 November 2011
DATES AMENDED:	Version 2: 19 November 2012 Version 3: 18 March 2013 Version 4: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	11-Nov-2016 20:30:25

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Changes to the protocol, along with a rationale for each change, are summarized below:

- The protocol title page was updated to align with current Sponsor practices. The Medical Monitor and the primary and secondary contacts for the study were updated.
- The guidelines for additional follow-up of patients beyond the Safety Follow-up visit (performed 4 weeks after the last dose of study treatment) were revised to include "or investigator's routine practice" for consistency in Section 3.1, Section 4.5.1.3, Section 4.5.1.8, Section 4.5.2.2, and Section 5.1.1 and the Schedule of Assessments in Appendix 1.
- The concomitant medications monitored after the Safety Follow-up visit were clarified in Section 3.4.2, Section 4.4, Section 4.5.2.4, and the Schedule of Assessments in Appendix 1 to include breast cancer treatments (e.g., endocrine therapy), anti-cancer treatments given to treat breast cancer recurrence, and medications related to the treatment of serious adverse events (SAEs) for consistency and clarity.
- As noted in the Note to File (dated 30 September 2016), an inconsistency was noted in the following sections of Protocol MO28040, Version 3: Section 4.5.2.4, Section 5.3.1, and Appendix 1, Footnote (l). Changes were made to maintain consistency between Section 4.5.2.4 and Section 5.3.1.
- The term "Study Completion/Early Discontinuation eCRF" was updated to "Death eCRF page" in Section 5.3.5.7 to maintain consistency between the protocol and the eCRF.
- The Herceptin (RO 45-2317, Trastuzumab) Investigator's Brochure was clarified as the primary reference safety information for determining the expectedness of adverse events in Section 5.7.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 4: SUMMARY OF CHANGES

GLOBAL CHANGES

The Medical Monitor has been changed to [redacted], Ph.D.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2.2.3.2: Study BO22227 (HannaH)

Study BO22227 ~~was~~*is* a Phase III, randomized, open-label, multicenter trial involving 596 female patients with HER2-positive early breast cancer in which the pharmacokinetics, efficacy, and safety of trastuzumab SC were compared with IV trastuzumab. Co-primary endpoints are serum C_{trough} pre-surgery and pathological complete response (pCR).

SECTION 2.3: EXPLORATORY OBJECTIVES

~~Two a~~*A*dditional, exploratory objectives will be investigated in a subset of patients (**Cohort B**) at selected study sites:

SECTION 3.1: DESCRIPTION OF STUDY

Patients will undergo a Safety Follow-up visit 4 weeks after their last dose of study treatment, with further follow-up according to the American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006) *or investigator's routine practice.* All patients will be followed-up for cancer recurrence and survival until study end. The duration of follow-up will be at least 5 years after their last study treatment, unless one of the following occurs first: withdrawal of consent, loss to follow-up, or death. After disease progression, patients will be managed as per local practice and followed for survival only.

SECTION 3.4.2: Safety Outcome Measures

The safety outcome measures for this study are as follows:

- All concomitant medication will be recorded between the Screening and the Safety Follow-up visits. Thereafter, ~~only medication applicable for long term reporting will be recorded including~~ breast cancer treatments (e.g., endocrine therapy), anti-cancer treatments given to treat a recurrence, and medications related to the treatment of SAEs ~~that are applicable for long term reporting (e.g., treatment of heart failure)~~ *will be recorded*.

SECTION 4.4: CONCOMITANT THERAPY

All concomitant medications are to be reported until the Safety Follow-up visit. Thereafter, only ~~medication applicable for long term reporting~~*the following medications* must be reported~~, including~~:

- Breast cancer treatments (e.g., hormonal therapy)
- Anti-cancer treatments given to treat a recurrence

- Medications related to the treatment of serious AEs~~that are applicable for long-term reporting (e.g., treatment of heart failure).~~

SECTION 4.5.1.3: Physical Examinations

A general physical exam (including a general neurological exam, as clinically indicated) will be performed at screening, approximately 3-monthly during trastuzumab SC treatment (at Week 13/Cycle 5, Week 25/Cycle 9, Week 37/Cycle 13, and Week 52/Cycle 18), at the post-treatment Safety Follow-up visit, and subsequently according to the ASCO 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006) *or investigator's routine practice.* Physical examinations will be performed according to local practice; however, particular attention should be given to the cardiovascular system.

SECTION 4.5.1.8: Breast Cancer Evaluations and Follow-Up

Patients will be assessed for residual disease (as per institutional practice) not more than 4 weeks before the first dose of study drug. Screening radiologic examinations to exclude metastatic disease should include a bilateral mammogram or breast MRI, and chest X-ray (CXR) or breast ultrasound. Should a previously taken chest CT or PET scan be available, then these results can also be used for eligibility assessment. These imaging tests do not need to be repeated if completed within 12 months prior to the first study treatment. In addition, bone scan and liver imaging should be performed if clinically indicated. During study treatment and the post-treatment follow-up period, patients will be followed for disease recurrence according to ~~the investigator's routine practice or~~ the American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up (Khatcheressian et al. 2006) *or investigator's routine practice* (see Appendix 1, Schedule of Assessments).

SECTION 4.5.2.4: Post-treatment Follow-up Visits (minimum 5 years)

All patients will be followed-up for cancer recurrence and survival till study end (i.e., until all patients have had a minimum 5-year follow-up) yearly or at higher frequency based on the site standard of care. The duration of follow-up will be at least 5 years after the last study treatment or until withdrawal from the study, lost to follow-up, or death, whichever occurs first. During this post-treatment follow-up period, patients will undergo the following assessments:

- Breast cancer follow-up according to the ASCO 2006 Guideline for Breast Cancer Follow-up (Khatcheressian et al. 2006) and reporting every 6 months or as per institutional standard practices (see Section 4.5.1.8 for details)
- Blood samples for immunogenicity and PK analyses will be collected from a subset of **Cohort B** patients (at selected sites only) 6 months after their last study treatment.
- Patients' weight must also recorded 6 months after their last study treatment if participating to immunogenicity and PK testing.
- Pregnancy test as clinically indicated up to ~~6~~*7* months after last study treatment

- AE follow-up: *After initiation of study drug,* all AEs/SAEs (except unrelated non-cardiac AEs in the follow-up period), regardless of relationship to study drug, will be reported until study closure. The investigator does not need to actively monitor subjects for AEs once the trial has ended. However, if becoming aware of any serious adverse events and non-serious adverse events of special interest occurring to a subject, the investigator should report those to the sponsor (see Section 5.6).
- Concomitant medications: Only ~~medication applicable for long-term reporting must~~*breast cancer treatments (e.g., endocrine therapy), anti-cancer treatments given to treat a recurrence, and medications related to the treatment of SAEs will* be ~~reported~~*recorded*; refer to Section 4.4 for details.
- Cardiac safety assessments will be performed at 6, 12, and 24 months and at yearly intervals until 5 years after treatment cessation (see Section 5.1.1.2 for details);
- Survival: After disease progression, patients will be managed as per local practice and followed for survival only.

After study treatment completion (or early discontinuation), AEs should be followed as outlined in Section 5.5 and Section 5.6.

Please see Appendix 1 for the schedule of follow-up assessments.

SECTION 5.1.1: General Safety Assessments

Patients will be assessed by prior medical history, vital signs (including blood pressure, heart rate, temperature), weight and height (screening only), physical examination, adverse events, and concomitant medications. A complete medical history (including demographic profile and prior treatments for cancer) will be documented at screening. A general physical exam (including general neurological exam, as clinically indicated) will be performed at screening, approximately 3-monthly (every 4 cycles) during trastuzumab SC treatment, at the post-treatment Safety Follow-up visit, and subsequently according to the ASCO 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006) *or investigator's routine practice* during the 5-year follow-up period (see Appendix 1, Schedule of Assessments). During physical examination, particular attention should be given to the cardiovascular system. Apart from physical exams, SC injection sites will be checked at every visit, and blood pressure will be measured before and after trastuzumab SC administration every 4 cycles, as specified in Appendix 1, Schedule of Assessments.

SECTION 5.3.1: Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported

(e.g., serious adverse events related to invasive procedures such as biopsies). All other adverse events will be recorded as medical history.

After initiation of study drug, all AEs/SAEs *(except unrelated non-cardiac AEs in the follow-up period)*, regardless of relationship to study drug, will be reported until study closure. The investigator does not need to actively monitor subjects for AEs once the trial has ended. However, if becoming aware of any serious adverse events and non-serious adverse events of special interest occurring to a subject, the investigator should report those to the Sponsor (see Section 5.6).

Any injection-site reactions are considered to be related AEs/SAEs and should be reported accordingly.

Symptomatic congestive heart failure must be reported irrespective of causal relationship during the full course of the study, even if the patient starts a new anticancer regimen.

SECTION 5.3.5.7: Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur prior to study closure that are attributed by the investigator solely to progression of EBC should be recorded only on the ~~Study Completion/Early Discontinuation~~ *Death* eCRF *page*. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

During study survival follow-up, deaths attributed to progression of EBC should be recorded only on the ~~Survival eCRF or Study Completion/Early Discontinuation~~ *Death* eCRF *page*.

SECTION 5.4.1: Emergency Medical Contacts
Medical Monitor (Roche Medical Responsible) Contact Information

Primary Contact

Medical Monitor: [redacted] M.D.

~~Address: F. Hoffmann-La Roche Ltd.~~

~~[redacted]~~

~~4070 Basel, Switzerland~~

Telephone No.:~~[redacted]~~

Mobile Telephone No.:~~[redacted]~~

Secondary Contact

Medical Monitor: Dr. [redacted] M.D.~~, PhD~~

~~Address:~~ [redacted]

~~[redacted], Belgium~~

Telephone No.: [redacted] *+650 225-1000*

~~Mobile~~*Office* Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Centre Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Centre Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

SECTION 5.4.3.1: Pregnancies in Female Patients

For women of childbearing potential (defined as premenopausal, less than 1 year after the onset of menopause or not surgically sterilized), appropriate contraceptive measures are mandatory during study treatment (see Section 4.5.1.7.3). Based on pharmacokinetic considerations, contraceptive measures are recommended for at least 7 months following the last dose of trastuzumab.

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within ~~6~~*7* months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue the study drug and counsel the patient, discussing the

risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the pregnancy, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). As soon as the EDC system is operating, the Pregnancy Report eCRF will be completed.

SECTION 5.4.3.2: Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within ~~6~~7 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

SECTION 5.5.1: Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

The Investigator must report new significant follow-up information for these events to the Sponsor within 24 hours after becoming aware of the information. New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event (including outcome of a reported pregnancy, as applicable)

In an individual patient, AE follow-up will continue as follows:

Related *or cardiac* AEs and SAEs will be followed until one of the following occurs:

- Resolved or improved to baseline state
- Relationship is reassessed as unrelated
- Investigator confirms that no further improvement can be expected
- Start of a new anti-cancer regimen
- Death

Unrelated *non-cardiac* AEs ~~severe or life threatening~~ *(Grade 3 or Grade 4)* and SAEs *(any grade)* will be followed until one of the following occurs:

- Resolved or improved to baseline state
- Severity improved to Grade 2
- Investigator confirms that no further improvement can be expected
- Start of new anti-cancer regimen
- Death

Unrelated *non-cardiac* AEs (Grade 1 or Grade 2) will be followed until 4 weeks after the last dose of study drug in an individual patient.

The final outcome of each adverse event must be recorded on the eCRF.

Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range or baseline state and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

SECTION 5.6: POST-STUDY ADVERSE EVENTS

At the ~~safety~~*final* follow-up visit *of the study*, the Investigator should instruct each patient to report to the Investigator any subsequent adverse events. The Sponsor should be notified if the Investigator becomes aware of any death or serious adverse event *related to study drug,* occurring at any time, after a patient has discontinued study participation, even after study closure~~, regardless of relationship to treatment of study drug~~. The investigator is not required to actively monitor patients after the study has ended.

The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The Investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the Investigator should report these events, indefinitely, directly to Roche Safety Risk Management via telephone (see "Protocol Administrative and Contact Information & List of Investigators").

SECTION 5.7: EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, AND ETHICS COMMITTEES

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document~~(s)~~:

- Herceptin (RO 45-2317, Trastuzumab) IB
- ~~Local prescribing information for Herceptin~~
- ~~Herceptin Core Data Sheet~~

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

SECTION 6.5.1: Secondary Efficacy Variables

Secondary efficacy endpoints include disease-free survival (DFS) and overall survival (OS) and will be assessed in both cohorts.

- DFS is defined as the time from the date of first treatment to the date of local, regional, or distant recurrence; contralateral invasive breast cancer (including ~~second primary non-breast cancer or~~ contralateral or ipsilateral ductal carcinoma in situ [DCIS]); or death due to any cause.
- OS is defined as time from the date of first treatment until date of death, regardless of the cause of death.

DFS and OS will be analyzed as a time-to-event variable for the ITT population (see Section 6.5.2).

In addition, patients' satisfaction with trastuzumab SC administration using the SID will be evaluated for **Cohort B** patients who went on to self-administration only.

SECTION 6.5.2: Analyses of Efficacy Endpoints

The efficacy endpoints, DFS and OS, will be analyzed as a time-to-event variable for the ITT and PP populations and for each cohort. Estimates and corresponding 95% confidence intervals for the survivor function for the time-to-event variable will be obtained by using the KM approach. A frequency table will be also provided for the type of DFS event (e.g., local, regional, or distant recurrence; contralateral *breast cancer*; or death).

A preliminary analysis of efficacy (DFS and OS) will take place when all patients have received 18 cycles of trastuzumab SC and have completed the post-treatment Safety Follow-up assessments. The final analysis of OS and DFS will take place when the last patient has been followed up for at least 5-years after her/his last study treatment, or earlier, if one of the following is documented for all treated patients: withdrawal of consent, loss to follow-up, or death. This is expected to take place approximately 8 years after the enrollment of the first patient, based on an expected 18-month recruitment period per cohort, 12 months of study treatment, and 5 years of follow-up after the last study treatment

Patients' satisfaction with trastuzumab SC administration using the SID (**Cohort B** patients who went on to self-administration only) will be summarized by frequency tables and presented graphically.

APPENDIX 1: Schedule of Assessments

The Schedule of Assessments has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III PROSPECTIVE, TWO-COHORT NON-RANDOMIZED, MULTICENTER, MULTINATIONAL, OPEN-LABEL STUDY TO ASSESS THE SAFETY OF ASSISTED- AND SELF-ADMINISTERED SUBCUTANEOUS TRASTUZUMAB AS THERAPY IN PATIENTS WITH OPERABLE HER2-POSITIVE EARLY BREAST CANCER [SafeHer Study]**
PROTOCOL NUMBER:	MO28048
VERSION NUMBER:	4
EUDRACT NUMBER:	2011-005328-17
IND NUMBER:	Not applicable
TEST PRODUCT:	Trastuzumab SC (RO 45-2317)
MEDICAL MONITOR:	[redacted], *Ph.D*
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III PROSPECTIVE, TWO-COHORT NON-RANDOMIZED, MULTICENTER, MULTINATIONAL, OPEN-LABEL STUDY TO ASSESS THE SAFETY OF ASSISTED- AND SELF-ADMINISTERED SUBCUTANEOUS TRASTUZUMAB AS THERAPY IN PATIENTS WITH OPERABLE HER2-POSITIVE EARLY BREAST CANCER [SAFEHER STUDY]**
PROTOCOL NUMBER:	MO28048
VERSION NUMBER:	4
EUDRACT NUMBER:	2011-005328-17
IND NUMBER:	Not applicable
TEST PRODUCT:	Trastuzumab SC (RO 45-2317)
PHASE:	Phase III
INDICATION:	HER2-positive early breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

Primary Objective

The primary objective of this study is to assess the overall safety and tolerability of trastuzumab subcutaneous (SC) in HER2-positive early breast cancer (EBC) patients with assisted administration using a conventional syringe and needle (vial formulation) or with assisted- and self-administration using a single-use injection device (SID) in selected patients.

Secondary Objectives

Secondary objectives include the evaluation of the following parameters:

- Efficacy (both cohorts):
  - Disease-free survival (DFS)
  - Overall survival (OS)
- Patient satisfaction with trastuzumab SC administration using the SID (patients in **Cohort B** who went on to self-administration of the study drug).

Exploratory Objectives

Additional, exploratory objectives will be investigated in a subset of patients (Cohort B) at selected study sites:

- To assess the immunogenicity of trastuzumab and recombinant human hyaluronidase (rHuPH20)
- To examine and characterize tolerability of the trastuzumab SC over a 6 hour time period after the start of the first administration and over a 2 hour time period after the start of subsequent trastuzumab administrations (only in patients using the SID **Cohort B**])
- Monitoring of SID usability in a subgroup of 48 patients in **Cohort B**

In addition, in some countries and sites, Medical Care Utilization (MCU, e.g. time and motion) and/or pharmacoeconomic substudies will be conducted. Details of the substudies will be described in separate protocols.

Study Design

This is a Phase III, prospective, two-cohort, non-randomized, multicenter, multinational, open-label study in approximately 2500 patients with HER2-positive EBC who are eligible for anti-HER2 therapy.

Eligible patients will be allocated to **Cohort A** or **B** at the investigator's discretion depending upon availability of the cohorts for recruitment:

- **Cohort A** (approximately 1,800 patients): trastuzumab SC 600 mg assisted administration into the thigh over a period of approximately 5 minutes using conventional handheld syringes with hypodermic needles for a total of 18 cycles (3-weekly);
- **Cohort B** (approximately 700 patients): trastuzumab SC at a fixed dose of 600 mg presented in a SID. The first administration will be assisted (performed by a HCP). If well tolerated and if the patient is willing and judged competent by the HCP to do so, subsequent administrations may be self-administered into the thigh over a period of approximately 5 minutes using the SID for a total of up to 18 cycles (3-weekly).
- Patients will remain at the study site to be observed for a period of 6 hours after their first trastuzumab administration and 2 hours thereafter for subsequent trastuzumab administrations. Patients may be required to remain onsite for an extended period of time if considered clinically necessary by the Investigator.

Description of Study

All potential study patients must provide signed written informed consent (approved by the relevant independent Ethics Committee [EC]) before undergoing any study-specific procedure. Results of the screening assessments must be available, and patients must meet all eligibility criteria prior to enrollment into the study.

During trastuzumab SC therapy, patients will be assessed for safety and efficacy.

In addition to efficacy and safety assessments, select sites will also perform immunogenicity testing to determine whether HAHAs against trastuzumab or rHuPH20 develop in patients receiving trastuzumab SC using the SID.

Patients will undergo a Safety Follow-up visit 4 weeks after their last dose of study treatment, with further follow-up according to the American Society of Clinical Oncology 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting *or investigator's routine practice*. All patients will be followed-up for cancer recurrence and survival until study end. The duration of follow-up will be at least 5 years after their last study treatment, unless one of the following occurs first: withdrawal of consent, loss to follow-up, or death. After disease progression, patients will be managed as per local practice and followed for survival only.

In some countries and sites, MCU (e.g., time and motion) and/or pharmacoeconomic substudies will be conducted. Details of the substudies will be described in separate protocols.

Number of Patients

Approximately 2500 patients will be enrolled into the study. The trial will be conducted at approximately 520 centers in approximately 60 countries.

Target Population

The study will recruit adult consenting patients with newly diagnosed HER2-positive (IHC 3+ or HER2-positive in situ hybridization [ISH]) early breast cancer who are eligible for treatment with trastuzumab (e.g., clinical Stage I [T1, N0, M0] to IIIC [any T, N3, M0]). Patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low-risk node-negative tumors $\leq$1.0 cm, elderly patients ($>$65 years of age), or patients who refuse chemotherapy, will also be eligible to participate in the study, but their enrollment will be limited to approximately $\leq$10% of the total study population.

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed written informed consent approved by the reviewing independent Ethics Committee (EC)
2. Female or male aged 18 years or above
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
4. Histologically confirmed early invasive HER2-positive carcinoma of the breast with no evidence of residual, locally recurrent, or metastatic disease and defined as clinical Stage I (T1, N0, M0) to IIIC (any T, N3, M0) that is eligible for treatment with trastuzumab

   Note: Patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low-risk node-negative tumors ≤ 1.0 cm, elderly patients (> 65 years of age), or patients with HER2-positive EBC but denying chemotherapy, will also be eligible to participate in the study, but their enrollment will be limited to approximately ≤ 10% of the total study population.
5. HER2-positive EBC, defined as IHC 3+ or positive in situ hybridization (ISH testing) by validated and approved methods within a certified laboratory
6. Screening left ventricular ejection fraction (LVEF) ≥ 55% as measured by echocardiography, multi-gated acquisition (MUGA) scan, or Magnetic Resonance Imaging (MRI) per local practice
7. Agreement to use an adequate, nonhormonal means of contraception by women of childbearing potential (defined as premenopausal and not surgically sterilized or < 1 year after the onset of menopause) and by male participants with partners of childbearing potential only. Examples of adequate contraceptive measures are an intrauterine device, a barrier method (condoms or diaphragm) in conjunction with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are not acceptable for females participating in the study.
8. Intact skin at site of SC injection on the thigh

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

Cancer-Related Criteria

1. Previous neoadjuvant or adjuvant breast cancer treatment with an approved or investigational anti-HER2 agent
2. History of other malignancy which could affect compliance with the protocol or interpretation of results (including previous invasive ipsilateral or contralateral breast cancer). Patients with curatively-treated carcinoma in situ of the cervix or basal cell carcinoma and patients with other curatively-treated malignancies other than breast cancer who have been disease-free for at least 5 years are eligible.

3. Past history of ductal carcinoma in situ (DCIS) within the last 5 years that has been treated with any systemic therapy OR with radiation therapy to the ipsilateral breast where invasive cancer subsequently develops. Patients who had their DCIS treated with surgery only are allowed to enter the study.
4. Metastatic disease

Hematological, Biochemical, and Organ Function

5. Inadequate bone marrow function (as indicated by any of the following):
   - Total white blood cell count (WBC) $< 2500/mm^3$ ($< 2.5 \times 10^9/L$)
   - Neutrophil count $< 1500/mm^3$ ($< 1.5 \times 10^9/L$)
   - Platelets $< 100{,}000/mm^3$ ($< 100 \times 10^9/L$)
   - Hemoglobin < 10 g/dL
6. Impaired hepatic function (as indicated by any of the following):
   - Serum total bilirubin $> 1.5 \times$ upper limit of normal (ULN)
   - Alanine amino transferase (ALT) $> 2.5 \times$ ULN
   - Aspartate amino transferase (AST) $> 2.5 \times$ ULN
   - Alkaline phosphatase (ALP) $> 2.5 \times$ ULN
7. Impaired renal function, as indicated by serum creatinine $> 1.5 \times$ ULN

Other Study Drug-Related Exclusion Criteria

8. Serious cardiac illness or medical conditions including but not confined to:
   - History of documented heart failure or systolic dysfunction (LVEF $< 50\%$)
   - High-risk uncontrolled arrhythmias such as atrial tachycardia with a heart rate > 100/min at rest, significant ventricular arrhythmia (ventricular tachycardia), or higher-grade atrioventricular (AV) block (second-degree AV block Type 2 [Mobitz 2] or third-degree AV block)
   - Angina pectoris requiring anti-anginal medication
   - Clinically significant valvular heart disease
   - Evidence of transmural infarction on electrocardiogram (ECG)
   - Poorly controlled or uncontrolled hypertension (blood pressure consistently over 140/90 mmHg, despite treatment) or history of hypertensive crisis or hypertensive encephalopathy
9. Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness
10. Prior maximum cumulative dose of doxorubicin > 360 mg/m2 or maximum cumulative dose of epirubicin > 720 mg/m2 or equivalent
11. Known hypersensitivity to trastuzumab, murine proteins, or excipients, or a general hypersensitivity to adhesives (Cohort B only)
12. History of severe allergic or immunological reactions, for example, difficult to control asthma.

General Exclusion Criteria

13. Pregnancy or lactation
14. Unable or unwilling to comply with the requirements of the protocol, as assessed by the investigator
15. Concurrent enrollment in another clinical trial using an investigational anti-cancer treatment, including hormonal therapy, bisphosphonate therapy, and immunotherapy, within 28 days prior to the first dose of study treatment
16. Major surgical procedure or significant traumatic injury within 14 days prior to the first dose of study treatment or anticipated need for major surgery during the course of study treatment except for breast cancer surgery for patient receiving study drug in the neoadjuvant setting. Patients must be free of any clinically significant sequelae of prior surgery before they can receive their first dose of study treatment.
17. More than 12 weeks between the end of the last chemotherapy cycle and the first dose of study treatment, in case these treatments are initiated sequentially. This criterion does not apply to patients who are starting trastuzumab SC without previous or concurrent chemotherapy or concurrently with chemotherapy.
18. Current peripheral neuropathy of Grade 3 or greater per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0

No exceptions or waivers will be granted for the above listed inclusion and exclusion criteria.

Length of Study

The study is estimated to last approximately 8 years, based on an expected 18-month recruitment period per cohort, 12 months of study treatment and 5 years of follow-up after the last study treatment.

To allow for the enrolment of 1800 patients in **Cohort A** (compared to 700 in **Cohort B**), recruitment for **Cohort A** may be initiated earlier than recruitment for **Cohort B**.

End of Study

End of study is defined as the last patient last visit in the follow-up period. The study will end when all patients have been followed for approximately 5 years after their last study treatment, or earlier, if one of the following is documented for all treated patients: withdrawal of consent, loss to follow-up, or death. The final analysis of OS and DFS and updated summaries for safety parameters will be performed at this stage.

Safety Outcome Measures

All clinical adverse events (AEs) and serious adverse events (SAEs), as well as abnormal laboratory values, will be recorded and graded according to the NCI-CTCAE version 4.0.

Cardiac function will be evaluated by measuring LVEF (using echocardiography, Multi Gated Acquisition (MUGA) scan or Magnetic Resonance Imaging [MRI]) and ECG. Symptomatic left ventricular dysfunction (CHF) will be graded according to NCI-CTCAE, version 4.0 and the NYHA functional classification.

Patients will undergo a Safety Follow-up visit 4 weeks after their last dose of study treatment with further follow-up according to the American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting *or investigator's routine practice*. All concomitant medication will be recorded between the Screening and the Safety Follow-up visits. Thereafter, breast cancer treatments (e.g., endocrine therapy), anti-cancer treatments given to treat a recurrence, and medications related to the treatment of SAEs *will be recorded*.

Efficacy Outcome Measures

DFS is defined as time from the date of first treatment to the date of local, regional, or distant recurrence; contralateral breast cancer; or death due to any cause.

Trastuzumab—F. Hoffmann-La Roche Ltd
24/Protocol MO28048, Version 4

OS is defined as time from the date of first treatment until date of death, regardless of the cause of death.

Patients in **Cohort B**, who went on to self-administration of the study drug will be asked to rate their overall satisfaction with trastuzumab SC administrations using the SID by completing a 5-item SID satisfaction questionnaire. The questionnaire will be completed after the 4th cycle and at the Safety Follow-up visit (or at least 1 day after the last trastuzumab SC injection), after a minimum of 2 successful self-administrations of the study drug.

Exploratory Outcome Measures

Immunogenicity of trastuzumab and rHuPH20 will be tested in a subset of patients enrolled in **Cohort B** at select sites. Serum samples (for anti-trastuzumab antibody analysis) and plasma samples (for anti-rHuPH20 antibody analysis) will be drawn at baseline (after eligibility is confirmed, i.e., just before the first study treatment), on-treatment (pre-Cycle 9 dose, Week 25), and at least 6 months after the end of treatment for testing in a central laboratory.

The exploratory MCU and/or pharmacoeconomic parameters will be described in separate substudy protocols.

In addition to the study assessments, all clinical AEs that occur during the observation period will be collected for all patients in **Cohort B** (within 6 hours after start of the first trastuzumab administration or within 2 hours (within 6 hours after start of the first trastuzumab administration or within 2 hours after start of following trastuzumab administrations). Data collected during the observation period will include: Frequency, incidence, and grade of AEs; onset and resolution times of AEs (dd:mm:yyyy:hh:mm); outcome of AEs; and details of treatments provided following AEs during the observation period.

Information on the usability of the SID will be collected via SID monitoring questionnaire, will be provided to the first 48 patients enrolled in Cohort B who were judged able and were willing to self-administer remaining doses from the SID under direct observation of the HCP. The SID Device Observation is to be completed by HCPs.

Investigational Medicinal Products

The investigational medicinal product for this study is trastuzumab SC 600 mg, supplied as a vial and SID formulations.

Patients in both cohorts will receive a fixed dose of 600 mg trastuzumab SC throughout the study, administered 3-weekly for a total of 18 cycles, unless disease recurrence, unacceptable toxicity, or patient withdrawal necessitates earlier treatment cessation.

Trastuzumab SC treatment may be initiated:

- After completion of neoadjuvant or adjuvant chemotherapy (sequentially)
- In combination with neoadjuvant or adjuvant paclitaxel or docetaxel chemotherapy (concurrently)
- or without adjuvant chemotherapy
- or in combination with neoadjuvant chemotherapy followed by trastuzumab therapy for locally advanced (including inflammatory) disease or tumors >2 cm in diameter

For patients receiving trastuzumab SC with concurrent chemotherapy, trastuzumab SC must be administered first, followed by the administration of chemotherapy. Hormonal therapy and radiotherapy (if applicable) may be given concomitantly with trastuzumab SC, as per local guidelines.

All study treatment administrations will occur in a hospital setting as follows:

- **Cohort A**: Trastuzumab SC 600 mg will be injected subcutaneously by an HCP into the thigh over a period of approximately 5 minutes using a handheld syringe with a gauge 25 or 27 hypodermic needle.
- **Cohort B**: Trastuzumab SC 600 mg will be injected subcutaneously into the thigh over a period of approximately 5 minutes using the SID. The first administration will be assisted (performed by a HCP [physician or nurse]), and then following administrations may be self-administered into the thigh (if the patient is willing and judged competent by the HCP) over a period of approximately 5 minutes using the SID.

Non-Investigational Medicinal Products

Not applicable.

Statistical Methods

Primary Analysis

Safety endpoints are the primary objectives in this study and will include: all AEs, Grade ≥ 3 AEs, SAEs, AEs leading to premature discontinuation of study treatment, AEs causing interruption of trastuzumab SC, cardiac AEs, CHF-related SAEs, premature withdrawals from study and study medication, exposure to treatment, laboratory parameters, LVEF, vital signs, ECG, weight, and ECOG performance status.

The primary analyses of the safety endpoints will consist of summary results with 95% confidence intervals and descriptions. They will be performed for the safety population (SP) defined as all enrolled patients who received at least one dose of study medication. There will be two safety populations, one for each cohort (SP1 for **Cohort A** and SP2 for **Cohort B**). The safety endpoints will be summarized for each cohort and overall.

The primary analysis of the safety endpoints will take place when all patients have received 18 cycles of trastuzumab SC and have completed the Safety Follow-up assessments (4 weeks after their last dose of study treatment). The primary analysis of safety endpoints will take place when all patients have received 18 cycles of trastuzumab SC and have completed the post-treatment Safety Follow-up assessments. Updated summaries for safety parameters will be prepared when the last patient has been followed up for at least 5 years after her/his last study treatment, or earlier, if one of the following is documented for all treated patients: withdrawal of consent, loss to follow-up, or death. All safety summaries and analyses will be performed for **Cohort A** and for **Cohort B**. There is no formal statistical hypothesis comparing **Cohort A** and **Cohort B**, and there will be no adjustments for multiplicity of endpoint comparisons. The safety summaries and analyses will be summarized for each cohort and overall.

Secondary and Exploratory Analyses

Secondary efficacy endpoints include DFS, OS (both cohorts) and patients' satisfaction with trastuzumab SC administration using the SID (**Cohort B** patients who went on to self-administration only). Secondary efficacy endpoints will be analyzed for the Intent-to-Treat (ITT) population (defined as all patients enrolled in the study) and the Per-Protocol population (defined as all patients in the ITT population who have received at least one dose of study medication and did not have major protocol violations). Protocol violations necessitating exclusion from the Per-Protocol population will be described in the Statistical Analysis Plan (SAP).

A preliminary analysis of DFS and OS will be undertaken at the time of the primary safety analysis, i.e. when all patients **(Cohort A and Cohort B)** have received 18 cycles of trastuzumab SC and have completed the Safety Follow-up assessments (4 weeks after their last dose of study treatment). The final analysis of OS and DFS will take place when the last patient has been followed up for approximately 5 years after her/his last study treatment, or earlier, if one of the following is documented for all treated patients: withdrawal of consent, loss to follow-up or death. This is expected to take place approximately 8 years after the enrolment of the first patient, based on an expected 18-month recruitment period per cohort, 12 months of study treatment and approximately 5 years of follow- up after the last study treatment.

Patients' satisfaction with trastuzumab SC administration using the SID (**Cohort B)** patients who went on to self-administration only) will be summarized by frequency tables and presented graphically.

Exploratory study analyses of the immunogenicity of trastuzumab and rHuPH20 will be performed in a subset of patients enrolled in **Cohort B** at select sites, based on samples collected at baseline (just before the first study treatment), on-treatment (pre-Cycle 9 dose, Week 25) and at least 6 months after the end of treatment. The percentage of patients who develop anti-trastuzumab or anti-rHuPH20 antibodies or both will be presented. Serum trastuzumab concentration data will be used in the assessment of anti-trastuzumab antibodies.

Exploratory study analyses for all clinical AEs that occur during the observation period will be evaluated, analyzed and presented and further exploratory analysis will be performed for all

patients in **Cohort B** (within 6 hours after start of the first trastuzumab administration or within 2 hours after start of following trastuzumab administrations). Details of the analysis will be documented in the Statistical Analysis Plan (SAP) and will include the following:

- Analysis of frequency, incidence and grading of AEs during the observation period
- Analysis of time from last preceding administration of study drug to onset time of AE occurrence (dd:mm:yyyy:hh:mm) during the observation period
- Analysis of time to resolution (dd:mm:yyyy:hh:mm) and outcome of AEs observed during the observation period
- Analysis of treatments provided following AEs during the observation period

Exploratory analyses on the usability of the SID summarizing the parameters collected via SID monitoring questionnaire will be provided to the first 48 patients enrolled in **Cohort B** who were judged able, and were willing to self-administer remaining doses from the SID under direct observation of the HCP. The SID Device Observation is to be completed by HCPs.

Determination of Sample Size

A sample size of approximately 2500 patients is planned for this study with approximately 1800 patients enrolled in **Cohort A** and approximately 700 patients enrolled in **Cohort B**. There is no formal statistical hypothesis, hence all safety (primary) endpoints results will be presented by 95% confidence intervals and descriptively explained.

For the purpose of the estimation of sample size, the incidence/proportion of congestive heart failure (CHF)-related SAEs was chosen as a safety endpoint of primary interest. Based on an observed CHF-related SAE incidence rate of 4% and a sample size of 1800 patients in **Cohort A,** the upper limit of the 95% confidence interval for the incidence rate will be 5.0%. For **Cohort B**, the same CHF-related SAE incidence rate and a sample size of 700 patients will give an upper limit of the 95% CI of 5.7%. The estimation of the sample size is produced by the SAS program and nQuery Version 6.

In Cohort B only, exploratory analyses on the usability of the SID summarizing the parameters collected via SID monitoring questionnaire will be provided to the first 48 patients enrolled who were judged able, and were willing to self-administer remaining doses from the SID under direct observation of the HCP. A sample size of 48 patients using the SID for 17 cycles to self-administer a dose without assistance equates to sample of n = 816 dosing events. If 0 events occur in this sample of trials it can be stated with 99% confident it will be <1% in the true population. The Adjusted Wald Approximate lower-limit of one-sided confidence interval for binomial distributed proportions statistical model has been used.

Refer to the protocol and the SAP for further details.

Interim Safety Analyses

Three interim safety analyses are planned for the study, when approximately 500, 1000, and 2500 patients have received at least one trastuzumab SC injection.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the plasma concentration–time curve
BCIRG	Breast Cancer International Research Group
BUN	Blood urea nitrogen
CEA	Carcinoembryonic Antigen
CHF	Congestive heart failure
CI	Confidence interval
CISH	Chromogenic in situ hybridization
CL	Clearance
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CMF	Cyclophosphamide methotraxate fluoricil
CNS	Central nervous system
CR	Complete response
CRF	Case Report Form[s]
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computerized tomography
C_{trough}	Trough plasma concentration
CV%	Coefficient of variation
CXR	Chest X-Ray
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DISH	Dual inform in situ hybridization
EBC	Early breast cancer
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report form
EDC	Electronic data capture

EEA	European Economic Area
EFS	Event-free survival
EU	European Union
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
HAHA	Human anti–human antibodies
HCP	Health Care Professional
HER2	Human epidermal growth factor receptor-2
HR	Hazard ratio
HV	Healthy volunteers
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICF	Informed Consent form
ICMJE	International Committee of Medical Journal Editors
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IMP	Investigational medicinal product
IND	Investigational New Drug
INN	International Non-proprietary Name
IRR	Infusion-related reaction
ISH	In situ hybridization
ITT	Intent-to-treat
IU	International Units
IV	Intravenous(ly)
KM	Kaplan-Meyer (analysis method)
LVEF	Left ventricular ejection fraction
LVSD	Left Ventricular Systolic Dysfunction
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Image
MUGA	Multiple gated acquisition
NCCN	National Comprehensive Cancer Network
NCCTG	North Central Cancer Treatment Group
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSABP	National Surgical Adjuvant Breast Project
NYHA	New York Heart Association

OS	Overall survival
PD	Progressive disease or Pharmacodynamic
PS	Performance Status
PK	Pharmacokinetic(s)
PPK	Population Pharmacokinetic(s)
p.o.	Per os (oral administration)
q1w	Every week
Q3W	Every 3 weeks
rHuPH20	Recombinant humanized hyaluronidase
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard Deviation
SID	Single-use injection device
SISH	Automated silver enhanced in situ hybridization
SmPC	Summary of Product Characteristics
SSR	Six-monthly SUSAR report
SUSAR	Suspected unexpected serious adverse reactions
TCH	Taxol, Carboplatin and Herceptin
$T_{1/2}$	Half-life
TNM	Primary tumor/regional lymph nodes/distant metastasis
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
Vc	Volume of distribution of the central compartment
WBC	White blood count
WFI	Water for injection

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

1.1.1 Epidemiology

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women worldwide, with an estimated 1.4 million new breast cancer cases and 458,000 deaths in 2008 (Jemal et al. 2010). More than half of all cases occur in industrialized countries. It is estimated that about 361,000 women (27.3% of cancers in women) are diagnosed (Parkin et al. 2005), and around 131,900 die annually of breast cancer in Europe, with breast cancer remaining the major cause of death in women aged between 35 and 59 (Ferlay et al. 2007). In the United States, the number of newly diagnosed breast cancer cases was estimated to be 209,000 (13.7% of all cancers and 28.0% of cancers in women), and the number of breast cancer-related deaths estimated to be 40,200 (7.1% of all cancer deaths and 14.7% of cancer deaths in women) in the year 2010 (Jemal et al. 2010; Kris et al. 2010). In Europe and North America, most breast cancers are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread, and can be treated with curative intent. In Europe, around 79% are potentially operable (stage T1-3/N0/+M0), 7% are locally advanced (T4/Nx/M0), and 6% are metastatic (M1) at diagnosis (Sant et al. 2003; Verma et al. 2010).

1.1.2 The Role of HER2-Receptor Status

The human epidermal growth factor receptor 2 (HER2, HER2/neu, c-erbB-2) gene, first discovered in 1984 (Schechter et al. 1984), is localized to chromosome 17q and encodes a transmembrane tyrosine kinase receptor protein that is a member of the epidermal growth factor receptor, or HER, family (Ross et al. 2009). This HER family of four receptors mediates the growth, differentiation and survival of cells (Yarden and Sliwkowski 2001; Gschwind et al. 2004). The evidence that increased expression and activity of HER2 induces cell transformation and tumorigenesis is overwhelming. In breast cancer, unlike a variety of other epithelial malignancies, HER2 gene amplification is uniformly associated with HER2 (p185neu) protein overexpression.

HER2 gene amplification and/or protein overexpression has been associated with aggressive tumor behavior, including increased cell proliferation, cell motility, tumor invasiveness, progressive regional and distant metastases, accelerated angiogenesis, and reduced apoptosis and poor prognosis (Ross et al. 2009; Slamon et al. 1987; Slamon et al. 1989; Sjögren et al. 1998; Moasser 2007; Ménard et al. 2001). A review of 107 studies involving 39,730 breast cancer patients found that in the majority (88%) of the studies, either HER2 gene amplification or HER2 (p185neu) protein overexpression predicted breast cancer outcome by either univariate or multivariate analysis (Ross et al. 2009). The frequency of HER2-positivity in these studies ranged from 9% to 74% (mean 22.2%). However, in current practice, most investigators report that the true HER2-positive rate is in the range of 15%–20% (Ross et al. 2009; Lund et al. 2010).

The major slide-based HER2 testing approaches include immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), automated silver enhanced in situ hybridization (SISH), and dual inform in situ hybridization (DISH) (all in situ techniques).

HER2-amplified breast cancers comprise a specific disease subset with a unique molecular portrait and biologic characteristics that distinguish them from other types of breast cancers (Moasser 2007; Crowe et al. 2006). Studies have shown that women whose tumors exhibit either amplification of the HER2 gene or overexpression of its encoded protein have a more aggressive form of breast cancer that is associated with significantly shortened disease-free and overall survival (OS) compared with women whose tumors do not over express HER2 (Dawood et al. 2010).

1.1.3 Treatment of Early Breast Cancer

Surgery is the main modality of local treatment for breast cancer (with or without radiotherapy) and can control loco-regional disease in the majority of patients. However, a significant percentage of patients relapse after loco-regional treatment and develop metastases. Systemic chemotherapy (or endocrine therapy in hormone receptor-positive patients) reduces the risk of relapse and is given either prior to surgery (neoadjuvant therapy) or following surgery (adjuvant therapy). In recent decades, the use of adjuvant systemic therapies for early breast cancer (EBC) has increased extensively and has most likely contributed to the substantial decline in breast cancer mortality observed in the U.S. and in some European countries (Verma et al. 2010; Colozza et al. 2006; Autier et al. 2010).

In the last few years, there has been accelerated progress in the treatment of EBC, with the introduction of taxanes and aromatase inhibitors and, most impressively, trastuzumab to the adjuvant portfolio (Colozza et al. 2006). Cytotoxic chemotherapy, endocrine therapy, radiotherapy, and molecular targeted therapies currently represent the backbone of modern systemic breast cancer treatment. Several targeted drugs with different molecular pathways have achieved approval for metastatic breast cancer (MBC), but trastuzumab is the only such therapy that is currently approved for adjuvant or neoadjuvant treatment of EBC (Untch 2010). The use of trastuzumab in the adjuvant setting is also supported by international treatment guidelines for women with HER2-positive breast cancer (NCCN 2010; Gnant et al. 2011; Aebi et al. 2011). The introduction of trastuzumab at the end of 1990s has particularly improved the outcome for early breast cancer patients with HER2-positive disease.

1.2 BACKGROUND ON TRASTUZUMAB

1.2.1 Intravenous Trastuzumab (Herceptin®)

Trastuzumab (Herceptin®) is a humanized monoclonal antibody directed against the extracellular domain of HER2. It is indicated for the treatment of patients with HER2-positive MBC (first approved in 1998) and EBC- (approved in 2005) and

HER2-positive metastatic gastric cancer (approved in 2010). The efficacy and safety of intravenous (IV) trastuzumab have been well characterized. Since its initial approval in 1998, trastuzumab has become standard of care for patients with HER2-positive breast cancer and is widely used for its approved indications in both the adjuvant and metastatic settings (Ross et al. 2009; NCCN 2010; Gnant et al. 2011; Aebi et al. 2011).

Intravenous trastuzumab is administered to EBC patients for a total duration of one year. Adjuvant trastuzumab IV may be given as monotherapy, starting after completion of adjuvant chemotherapy, or in combination with the taxane component of adjuvant chemotherapy (followed by trastuzumab monotherapy). At the time of writing, adjuvant trastuzumab IV monotherapy is widely approved, and concurrent administration in combination with adjuvant chemotherapy is also approved or expected to be approved in many countries. Intravenous trastuzumab may be given weekly (q1w) or 3-weekly (Q3W) to patients with MBC, but in the adjuvant setting, when given as monotherapy, it is generally given Q3W.

For the regulatory status and approved indications in specific countries, please refer to the current Herceptin (RO 45-2317, Trastuzumab) Investigator's Brochure (IB) and local prescribing information.

1.2.1.1 Pharmacokinetics of Trastuzumab IV

Based on a population pharmacokinetic (PK) analysis of data primarily from the metastatic breast cancer setting (Clinical Study Report 1018264), the predicted median AUC (over a period of 3 weeks at steady-state) for the q1w and Q3W regimens were 1677 and 1793 mg • day/L, respectively, and the corresponding median C_{min} values were 64.9 and 47.3 mg/L, respectively. A two-compartment model satisfactorily described the data. The typical trastuzumab IV PK parameters were as follows: clearance (CL) of 0.026 L/day and a volume of distribution of the central compartment (Vc) of 3.17 L (which corresponds to human plasma volume, which is the Vc characteristic of IgG immunoglobulins). The equilibrium half-life is about 26 days, which is similar to that of endogenous IgG1 immunoglobulin (23 days) which constitutes the backbone of trastuzumab IV.

Refer to the Herceptin (RO 45-2317, Trastuzumab) IB for further details regarding the pharmacokinetics of trastuzumab IV.

1.2.1.2 Efficacy of Trastuzumab IV in Early Breast Cancer (Adjuvant Setting)

Six Phase III, multicenter, randomized-controlled trials investigated the efficacy and safety of adjuvant trastuzumab IV in combination with or after standard adjuvant chemotherapy in the treatment of early breast cancer:

- Herceptin Adjuvant (HERA, BO16348) trial (Piccart-Gebhart et al. 2005; Smith et al. 2007; Gianni et al. 2011)

- North Central Cancer Treatment Group trial (NCCTG) N9831 trial (Romand et al. 2005; Perez et al. 2007; Perez et al. 2009; Perez et al. 2011)
- National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31 (Romand et al. 2005; Perez et al. 2007; Perez et al. 2009; Perez et al. 2011)
- Breast Cancer International Research Group (BCIRG-006) study (Slamon et al. 2009; Slamon et al. 2011)
- Protocol Adjuvant dans le Cancer du Sein (PACS04) trial (Spielmann et al. 2009)
- Finland Herceptin (FinHer) trial (Joensuu et al. 2009)

Together, these trials accrued more than 15,000 women with node-positive or high-risk node-negative breast cancer and used a variety of cytotoxic agents in various combinations, doses, and orders of administration. Four of these trials (HERA, N9831, B31, and BCIRG-006) are considered pivotal.

In the HERA study, trastuzumab treatment was started following completion of an approved neoadjuvant or adjuvant chemotherapeutic regimen (and radiotherapy as indicated) and continued for one or two years. In Studies B31, N9831, and BCIRG-006, trastuzumab started after completion of four cycles of doxorubicin/cyclophosphamide and was administered for one year, either concurrently with four cycles of taxane chemotherapy (B31, N9831), or concurrently with six cycles of a non-anthracycline-containing taxane-based regimen (BCIRG-006), or after completion of chemotherapy (see Table 1).

All four pivotal randomized controlled trials (HERA, N9831, B31, and BCIRG-006) demonstrated significantly improved disease-free survival (DFS), and three (HERA, B31 and BCIRG-006) demonstrated significantly improved overall survival (OS; see Table 1). The DFS benefits were observed regardless of age, nodal status, hormonal status, or tumor size in all trials (Gianni et al. 2011; Slamon et al. 2011; Perez et al. 2011). Importantly, the most recent follow-up data from the HERA trial (Gianni et al. 2011) and the combined analysis of the NCCTG N9831 and NASBP B-31 trials (Perez et al. 2011) both demonstrate consistent DFS and OS advantages of adjuvant trastuzumab over a median follow-up of 4 years. Further, the significant benefits in DFS and OS were maintained over a median follow-up of approximately 5 ½ years in the BCIRG-006 study (Slamon et al. 2011), which is the longest follow-up reported to date. The long-term clinical benefits of 1-year trastuzumab treatment clearly continue to outweigh the risks of adverse effects (Perez et al. 2011), and the regimen is considered standard of care with support from all major treatment guidelines (NCCN 2010; Gnant et al. 2011; Aebi et al. 2011).

Of the four pivotal randomized trials, the N9831 study was the only one to directly compare the concurrent and sequential use of trastuzumab. This study identified a strong trend for a 25% reduction in the risk of an outcome event when trastuzumab is started concurrently as compared to sequentially after paclitaxel (Perez et al. 2009).

Therefore, based on a positive risk/benefit ratio, the authors recommended that trastuzumab be incorporated in a concurrent fashion when administered with paclitaxel (Perez et al. 2009), which also resulted in the approval of the concurrent use of trastuzumab and chemotherapy.

For further details, refer to the current Herceptin (RO 45-2317, Trastuzumab) IB.

Table 1 Efficacy of Trastuzumab IV in the Adjuvant EBC Setting

Study	Median FU (mo)	Interventions	No. of Patients [a]	DFS	OS
SEQUENTIAL TRASTUZUMAB					
HERA (Piccart-Gebhart et al. 2005; Gianni et al. 2011) N = 5090	48	CT ± RT → OBS	1698	2-yr DFS: 81% 4-yr DFS: 72%	2-yr OS: 95% 4-yr OS: 88%
		CT ± RT → T (× 1 yr)	1703	2-yr DFS: 87% HR 0.64, p < 0.0001 4-yr DFS: 79% HR 0.76, p < 0.0001	2-yr OS: 97% HR 0.66, p = 0.012 4-yr OS: 89% HR 0.85, p = 0.11
		CT ± RT → T (× 2 yrs)	1701	NR	NR
NCCTG N9831 (Perez et al. 2009) N = 3505 (1097 sequential)	66	AC → P	1087	5-yr DFS: 72%	NR
		AC → P → T	1097 [b]	5-yr DFS: 80% HR 0.70, p = 0.0005	HR 0.86, p = 0.281
		AC → P + T → T	949	5-yr DFS: 84% HR 0.75, p = 0.019	NR
CONCURRENT TRASTUZUMAB					
NSABP B-31 (Perez et al. 2011) N = 2101	47	AC → P	1046	4-yr DFS: 72%	NR
		AC → P + T	1055	4-yr DFS: 85%	NR
B-31 + N9831 (Romond et al. 2005; Perez et al. 2007; Perez et al. 2011) N = 3351 [c]	47	AC → P	1679	3-yr DFS: 75% 4-yr DFS: 74%	3-yr OS: 92% 4-yr OS: 86%
		AC → P + T	1672	3-yr DFS: 87% 4-yr DFS: 86% HR 0.51, 95%CI: 0.44–0.59	3-yr OS: 94% 4-yr OS: 93% HR 0.59, 95%CI: 0.48–0.73

Table 1 Efficacy of Trastuzumab IV in the Adjuvant EBC Setting (cont.)

Study	Median FU (mo)	Interventions	No. of Patients [a]	DFS	OS
B-31 + N9831 (Romond et al. 2005; Perez et al. 2007; Perez et al. 2011) N = 3351 [c]	47	AC→P	1679	3-yr DFS: 75% 4-yr DFS: 74%	3-yr OS: 92% 4-yr OS: 86%
		AC→P+T	1672	3-yr DFS: 87% 4-yr DFS: 86% HR 0.51, 95%CI: 0.44–0.59	3-yr OS: 94% 4-yr OS: 93% HR 0.59, 95%CI: 0.48–0.73
BCIRG-006 (Slamon et al. 2009; Slamon et al. 2011) N = 3222	65	AC→D	1073	5-yr DFS: 75%	5-yr OS: 87%
		AC→D+T (×1 yr)	1074	5-yr DFS: 84% HR 0.64, p < 0.001	5-yr OS: 92% HR 0.63, p < 0.001
		D+Carbo+T (×1 yr)	1075	5-yr DFS: 81% HR 0.75, p = 0.04	5-yr OS: 91% HR 0.77, p = 0.04

AC = doxorubicin plus cyclophosphamide; Carbo = carboplatin; CEF = cyclophosphamide, epirubicin and fluorouracil; CI = confidence interval; CT = chemotherapy; D = docetaxel; DFS = disease-free survival; FU = follow-up; HR = hazard ratio; NSS = not statistically significant; OBS = observation; OS = overall survival; P = paclitaxel; RT = radiotherapy; T = trastuzumab.

[a] Number of patients denotes patients included in the efficacy analyses.

[b] Joint analysis of the NSABP B-31 and NCCTG N9831 trials.

[c] Excluded from the joint analysis by Romond et al. (Perez et al. 2007).

1.2.1.3 Safety of Trastuzumab IV

1.2.1.3.1 Cardiac Safety of Trastuzumab IV

The most clinically relevant adverse event (AE) associated with trastuzumab IV is left ventricular cardiac dysfunction (congestive heart failure or CHF). In patients with HER2-positive EBC enrolled in pivotal clinical trials described in Section 1.2.1.2, trastuzumab treatment for 1 year (administered concurrently or sequentially with chemotherapy) appeared to be associated with a decrease in LVEF, an increase in the incidence of CHF (where specified, this was severe [New York Heart Association or NYHA] Class III or IV, or Grade 3 or 4 or symptomatic CHF), and discontinuation of treatment as a result of cardiac adverse events (Garnock-Jones et al. 2010). Cardiac toxicity described as NYHA Class III/IV CHF occurred in 0%–0.9% of patients in the control arms and in 0%–3.8% of patients in the trastuzumab-containing arms of the four pivotal trials (see Table 2). However, the cardiotoxicity observed with concurrent or sequential trastuzumab treatment appeared to be mostly reversible following trastuzumab discontinuation, and no significant increase in cardiac death was reported (Garnock-Jones et al. 2010).

An overview of cardiac safety data from selected trials of trastuzumab in combination with a taxane after anthracyclines for HER2-overexpressing EBC shows rates of

symptomatic or severe CHF of < 4% and asymptomatic declines in left ventricular ejection fractions of > 10 percentage points in ≤ 30% of patients. However, interstudy comparisons of chemotherapy-induced cardiac dysfunction are difficult because of the use of different definitions of cardiac dysfunction and different parameters for assessing cardiac safety (Ewer and O'Shaughnessy 2007). These levels were considered below safety cut-off points set by the individual studies' independent data monitoring committees (Jahanzeb et al. 2008).

The NSABP B-31 trial determined the 5-year cumulative cardiac event rate (NYHA Class III or IV CHF or cardiac death) to be 3.8% in patients randomly assigned to trastuzumab versus 0.9% in patients who received chemotherapy alone (Rastogi et al. 2007; Russell et al. 2010). In the NCCTG N9831 trial, the incidence of CHF was 0% in the chemotherapy-alone arm, 2.2% in patients who received sequential chemotherapy and trastuzumab, and 3.3% in patients who received concurrent chemotherapy and trastuzumab (Perez et al. 2008). An independent adjudication of the cardiac events occurring in Studies B-31 and N9831 determined that the incidence of symptomatic heart failure events was 2.0% in trastuzumab-treated patients compared with 0.45% in the chemotherapy-alone arm, and that and the majority (86%) of these patients recovered with appropriate treatment (Russell et al. 2010).

The long-term incidence of cardiac AEs in patients with EBC who were treated with trastuzumab IV for 1 year after completion of neoadjuvant or adjuvant chemotherapy was also evaluated in the HERA trial. Of the 1698 patients randomly assigned to observation and 1703 randomly assigned to 1 year of trastuzumab treatment, 94% had been treated with anthracyclines. The incidence of discontinuation of trastuzumab because of cardiac disorders was low (5.1%). At a median follow-up of 3.6 years, the incidence of cardiac endpoints remained low, though it was higher in the trastuzumab group than in the observation group (severe CHF, 0.8% vs. 0.0%, respectively; confirmed significant LVEF decreases, 3.6% vs. 0.6%, respectively). In the trastuzumab group, 59 of 73 patients with a cardiac endpoint reached acute recovery (Procter et al. 2010).

Table 2 Cardiac Safety of Trastuzumab IV in the Adjuvant Setting

Study	Interventions	No. of Pts [a]	LVEF↓ from BL, % of pts	Symptomatic HF, % of pts
SEQUENTIAL TRASTUZUMAB				
HERA (Piccart-Gebhart et al. 2005; Gianni et al. 2011; Procter et al. 2010) N = 5090	CT ± RT → OBS	1698	Signif: 0.5%	0.1% (NYHA Class III/IV: 0)
	CT ± RT → T × 1 yr	1703	Signif: 3%	2% (NYHA Class III/IV: 0.6%)
	CT ± RT → T × 2 yrs	1701	NR	NR

Table 2 Cardiac Safety of Trastuzumab IV in the Adjuvant Setting (cont.)

NCCTG N9831 (Perez et al. 2009) N = 3133	AC→P AC→P→T	1087 1097	NR NR	NR Gr 3/4 or SCD: 2.8%
CONCURRENT TRASTUZUMAB				
NSABP B-31 (Perez et al. 2007; Tan-Chiu et al. 2005; Romond 2005; Rastogi et al. 2007) N = 2043	AC→P AC→P + T	872 864	NR NR	NYHA Class III/IV or SCD at 5 yrs: 0.9% NYHA Class III/IV or SCD at 5 yrs: 3.8%
NCCTG N9831 (Perez et al. 2009) N = 3133	AC→P AC→P + T→T	1087 949	NR NR	NR Gr3/4 or SCD: 3.3%
BCIRG-006 (Slamon et al. 2009; Slamon et al. 2011) N = 3222	AC→D AC→D + T (× 1 yr) D + Carbo + T (× 1 yr)	1073 1074 1075	↓ > 10%: 11% ↓ > 10%:19% ↓ > 10%: 9%	Gr3/4: 0.7% Gr3/4: 2.0% Gr3/4: 0.4%

AC = doxorubicin plus cyclophosphamide; BL = baseline; CEF = cyclophosphamide, epirubicin and fluorouracil; CT = chemotherapy; D = docetaxel; FU = follow-up; Gr = Grade (NCI-CTCAE); NR = not reported; NYHA = New York Heart Association (functional class); OBS = observation; P = paclitaxel; RT = radiotherapy; SCD = sudden cardiac death; Signif = significant drop in LVEF (symptomatic or asymptomatic); T = trastuzumab; yr = year.

Note: The assessments and definitions differed among the studies; therefore the data provided are not suitable for comparisons between trials.

[a] Number of patients denotes patients included in the analyses.

1.2.1.3.2 Post-marketing Safety Summary of Trastuzumab IV

It is estimated that over 1 million patients have been treated with trastuzumab IV as of October 2011 (Roche, Data on file).

The most common (occurring in ≥ 1 out of 10 treated patients) adverse reactions are infusion-associated symptoms such as fever and chills, usually following the first infusion of trastuzumab IV. These symptoms are usually mild to moderate in severity and occur infrequently with subsequent trastuzumab IV infusions in up to 40% of patients. Other very common (≥ 1 of 10 patients) adverse reactions include febrile neutropenia, tremor, dizziness, headache, blood pressure changes (increase or decrease), irregular heartbeat, palpitation, cardiac flutter, decreased ejection fraction, dyspnea, wheezing, diarrhea, vomiting, nausea, lip swelling, abdominal pain, erythema, rash, swelling of the face, arthralgia, muscle tightness, myalgia, asthenia, chest pain, fatigue, influenza-like symptoms, infusion-related reaction, and pain.

Some adverse reactions to trastuzumab IV infusion can be serious and include dyspnea, hypotension, elevated blood pressure, wheezing, bronchospasm, tachycardia, reduced

oxygen saturation, and respiratory distress. In the post-marketing setting, very rare (< 1 of 10,000 patients) occurrences of severe infusion reactions leading to a fatal outcome have been associated with the use of trastuzumab IV.

Severe pulmonary events leading to death have been reported with the use of trastuzumab IV in the post-marketing setting (4 out of 10,000 treated patients). Signs, symptoms, and clinical findings included interstitial lung disease including pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema, and pulmonary insufficiency. These events may or may not occur as sequelae of infusion reactions. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs resulting in dyspnea at rest may be at greater risk of severe reactions. Other risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies such as taxanes, gemcitabine, vinorelbine, and radiation therapy.

In addition, severe hypersensitivity reactions have been infrequently reported in patients treated with trastuzumab IV (the exact incidence of these events is unknown). Signs and symptoms include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions have been fatal. Symptom onset generally occurred during an infusion, but onset after the completion of an infusion has also been reported. Reactions were most commonly reported in association with the initial infusion.

The immunogenicity of trastuzumab IV has been investigated in clinical studies that included 903 MBC patients. Human anti–human antibodies (HAHA) to trastuzumab were detected in 1 patient, who had no allergic manifestations.

More detailed information on the full safety profile of trastuzumab IV is found in the Herceptin (RO 45-2317, Trastuzumab) IB.

1.2.2 Trastuzumab SC

Trastuzumab for subcutaneous (SC) administration has been developed by F. Hoffmann La Roche Ltd to address the known limitations of IV administration (e.g., infusion-related reactions, long administration times, requirement for hospital facilities, treatment barrier for patients with poor venous access, continued use of port-a-cath systems). Subcutaneous administration of trastuzumab takes significantly less time (up to 5 minutes) compared to IV infusion (30–90 minutes), and this is expected to improve treatment convenience and compliance. These attributes are particularly important for patients treated over prolonged periods of time, such as in the adjuvant setting. Subcutaneous administration offers the potential for self-administration of trastuzumab, which is expected to further improve treatment convenience and compliance.

1.2.2.1 Recombinant human hyaluronidase (rHuPH20)

The feasibility and patient acceptability of subcutaneous administration of any drug is dependent on the volume that must be administered. A key excipient in the SC formulation is the enzyme hyaluronidase, which enables larger volumes to be administered without reduced tolerability and patient acceptability. Animal-derived hyaluronidase has been available commercially for over 60 years and is used primarily as a permeation enhancer to increase the dispersion and absorption of other co-administered drugs. Hyaluronidase transiently hydrolyses hyaluronan, a component of the subcutaneous matrix, leading to reduced viscosity of the extracellular matrix of the hypodermis and, thus, to an improved delivery of SC administered drugs to the systemic circulation. The decreased viscosity is also expected to facilitate SC administration of larger volumes of fluid.

More recently, recombinant human hyaluronidase (rHuPH20) has been developed and approved to improve dispersion and absorption of co-administered drugs. This recombinant human molecule has a higher purity and is associated with improved efficacy and tolerability compared with the animal-derived enzyme. In the US, one recombinant humanized hyaluronidase, Hylenex® (Hylenex® Prescribing Information 2005), is licensed to facilitate the absorption and dispersion of drugs when given SC at doses between 50 IU and 300 IU (Frost 2007). The rHuPH20 used in the current study is produced from a second generation of the Hylenex® process, with an improved yield and purity. It has been combined with trastuzumab to allow safe and comfortable subcutaneous injection of volumes ≥3 mL.

1.2.2.1.1 Nonclinical Studies with rHuPH20

After IV administration in the dose range 0.3–30 mg/kg, rHuPH20 demonstrated nonlinear PK, rapid clearance, and a half-life of around 5 minutes at the lowest dose tested. The bioavailability of rHuPH20 following SC administration was extremely low (not determinable at low doses, 6%–8% in the dose range 3–30 mg/kg). Treatment of various species with rHuPH20 (IV or SC) was generally well tolerated, and no major abnormalities were noted in any toxicology studies.

For further details on nonclinical studies with rHuPH20 refer to the Herceptin (RO 45-2317, Trastuzumab) IB.

1.2.2.1.2 Clinical Studies with rHuPH20

Mammalian hyaluronidase preparations differing in source species and manufacturing processes have been the subject of multiple investigations and regulatory approvals in Europe, the US, and Asia. It is estimated that these products have been administered to tens of millions of patients in the US. The safety and efficacy of hyaluronidase products have been widely established. The most significant safety risk identified is hypersensitivity/allergenicity, which is thought to be related to the lack of purity of the animal-derived preparations (Frost 2007; Harris 2003). Humanized recombinant

hyaluronidase preparations are associated with an improved purity and corresponding decreased safety risk.

Clinical data are available from four studies with rHuPH20.

- In an allergic sensitivity study (Study R04-0851), 100 healthy volunteers were injected intradermally with 0.1 mL (15 U) of rHuPH20 and saline control. The most common side effects were generally mild redness, bruising, swelling, discomfort, and itching. No AEs were serious, and none were judged to be related to study treatment.
- A proof-of-concept dose-escalation study (Study HZ2-06-02) with adalimumab and rHuPH20 in 15 patients with rheumatoid arthritis evaluated the effects of rHuPH20 on the PK, safety, and tolerability of adalimumab. A single co-administration of adalimumab with rHuPH20 increased adalimumab exposure by a weighted average of 13% compared to adalimumab alone. The injection was well tolerated, with only mild and moderate AEs.
- Study HZ2-07-01 was a double-blind, within-subject-controlled, two-way cross-over trial comparing the time to inject (flow rate), safety, and tolerability of a SC administered 10% (2000 mg in 20 mL) solution of immunoglobulin G (diluted Carimune® NF) with and without rHuPH20 in 30 healthy volunteers. There was a statistically nonsignificant trend towards a decrease in time to inject and an increase in flow rate in the presence of rHuPH20 relative to the control group. The most common AEs were injection-site reactions consisting of erythema, pain, edema, induration, or pruritus (communication with Halozyme Therapeutics Inc. on preliminary study results).
- Study HZ2-07-02 investigated the SC injection of different rHuPH20 concentrations in a viscous solution of IgG and adalimumab in healthy volunteers using different volumes of injection (2, 8, and 16 mL). The maximum total enzyme dose administered in this study was 96,000 U. The injections were well tolerated, with no serious adverse events (SAEs) reported. All injection-site reactions, such as erythema, pain and induration, were mild (98%) or moderate (2%) in severity. There was a trend to lower mean time to inject in subjects who received rHuPH20 compared to those who received injections without rHuPH20, as well as a trend towards an increase in the exposure to adalimumab in the presence of rHuPH20. Pain increased across all volume cohorts after injection, with no clear difference between the presence and absence of rHuPH20.

The highest total rHuPH20 dose administered in these clinical studies was 96,000 U in Study HZ2-07-02, and this was well tolerated by healthy volunteers.

For further information on the clinical trials conducted with rHuPH20, refer to the Herceptin (RO 45-2317, Trastuzumab) IB.

1.2.2.2 Nonclinical Studies with Trastuzumab SC

An overview of completed nonclinical pharmacology, PK, and toxicology studies of trastuzumab SC is provided in Table 3. Overall, these studies showed that rHuPH20 enabled more rapid absorption of trastuzumab SC, and that SC administration of trastuzumab formulated with rHuPH20 was well tolerated locally and systemically.

For further information, refer to the Herceptin (RO 45-2317, Trastuzumab) IB.

Table 3 Overview of Completed Nonclinical Pharmacology, PK, and Toxicology Studies with Trastuzumab SC (Formulated with rHuPH20)

Study Type	Objective	Species	Key findings
Pharmacology			
In vivo efficacy in mouse xenograft model	Comparison of trastuzumab SC with trastuzumab IV	Mouse	Comparable efficacy providing similar trough levels achieved
Pharmacokinetics			
PK (non GLP)	Assessment of trastuzumab SC PK in preparation for efficacy/pharmacology study (above)	Mouse	Bioavailability of trastuzumab SC estimated at 83.4%
PK/dose finding	Optimization of trastuzumab SC formulation for clinical studies	Mini-pig	More rapid absorption of trastuzumab SC formulated with rHuPH20 than without rHuPH20
PK assessment	Assessment of trastuzumab SC PK in preparation for 13 week repeat dose toxicity study	Cynomolgus monkey	Maximum serum trastuzumab levels achieved 24 hours after trastuzumab SC (PK comparable to mini-pig)

AUC = area under the curve; GLP = Good Laboratory Practices; IV = intravenous;
PK = pharmacokinetic; rHUPH20 = recombinant humanized hyaluronidase; SC = subcutaneous.

Table 3 Overview of Completed Nonclinical Pharmacology, PK, and Toxicology Studies with Trastuzumab SC (Formulated with rHuPH20) (cont.)

Study Type	Objective	Species	Key findings
Toxicology			
Local tolerance	Clinical symptoms and injection site reactions following single dose trastuzumab SC	Rabbit	No signs of systemic toxicity. No macroscopic or microscopic findings attributable to treatment
13 week repeat dose toxicity	High dose toxicity, clinical symptoms, and injection site reactions	Cynomolgus monkey	Trastuzumab exposure (AUC) comparable to that achieved at highest doses in nonclinical IV safety program. No adverse findings for any of the parameters evaluated. Low immunogenicity (anti-trastuzumab antibodies found in 1 of 4 recovery animals)

AUC = area under the curve; GLP = Good Laboratory Practices; IV = intravenous; PK = pharmacokinetic; rHUPH20 = recombinant humanized hyaluronidase; SC = subcutaneous.

1.2.2.3 Clinical Studies with Trastuzumab SC

Subcutaneous trastuzumab (formulated with rHuPH20) has been studied in one completed clinical trial (BP22023, CP2) and one ongoing clinical trial (BO22227, HannaH) using conventional syringes and hypodermic needles for administration. In addition, a PK study (BO25532, CP3) now completed in healthy volunteers has demonstrated comparable exposure between SC administration with the single-use injection device (SID) versus with the conventional syringe and needle. Lastly, a patient satisfaction and health care professional (HCP) preference study (MO22982, PrefHer) comparing trastuzumab SC administration using SID and vial with trastuzumab IV administration is ongoing in parallel with the current study.

Table 4 Overview of the Clinical Development Program of Trastuzumab SC

Studies	Status	Design	Primary Objective
Trastuzumab SC (Vial)			
Phase Ib dose-finding study (BP22023, CP2)	Completed	Dose-finding/dose-confirmation study OL, PG, single-dose, MC	Select the dose of trastuzumab SC which results in comparable exposure to that achieved from an IV dose of trastuzumab
Phase III clinical study (BO22227, HannaH)	Ongoing	PK, efficacy, and safety study in the neoadjuvant/adjuvant setting OL, PG, randomized, multiple-dose, MC	Non-inferiority of pre-surgery trastuzumab C_{trough} and pCR
Phase I device qualification study (BO25532, CP3)	Ongoing	PK bridging to injection device OL, PG, randomized, single-dose, MC	Pharmacokinetic comparability of trastuzumab SC dosing via a SID or via hand-held needle and syringe used in previous clinical studies.
Additional Studies			
Phase II patient preference study (MO22982, PrefHER)	Ongoing	Patient preference and HCP satisfaction study Randomized, MC, cross-over study	To evaluate patient preference for trastuzumab SC administration using a SID or vial versus trastuzumab IV

HCP = health care professional; MC = multicenter; OL = open-label; pCR = pathological complete response; PG = parallel-group; PK = pharmacokinetic; SID = single-use injection device.

1.2.2.3.1 Study BP22023 (CP2)

Study BP22023 (Wynne et al. 2013) included two parts: trastuzumab SC dose finding in healthy male subjects and subsequent dose confirmation in female HER2-positive breast cancer patients. Twenty-four healthy male subjects and 46 female subjects with HER2-positive EBC received single doses of either trastuzumab IV or trastuzumab SC, as outlined in Table 5. The dose of rHuPH20 received depended on the volume administered, which depended on the body weight-based dose of trastuzumab. The concentration of trastuzumab in the SC formulation was 120 mg/mL. The concentration of rHuPH20 was 2000 U/mL.

Table 5 Summary of Treatment Cohorts and Adverse Events, Study BP22023

Cohort	Route of administration	Subjects	Dose (mg/kg)	AEs	
				Subjects n (%)	Events n [Gr1/Gr2/Gr3]
Part 1 (Dose finding)					
All Subjects				27 (90)	86 [61/24/1]
1	IV	6 healthy males	6	5	26 [19/6/1]
2	IV	6 HER2-positive EBC females	6	6	24 [17/7/0]
3	SC	6 healthy males	6	5	12 [9/3/0]
4	SC	6 healthy males	10	5	11 [8/3/0]
5	SC	6 healthy males	8	6	13 [8/5/0]
Part 2 (Dose confirmation)					
All subjects				39 (98)	181 [131/46/4]
A	SC	20 HER2-positive EBC females	8	19	87 [61/23/3]
B	SC	20 HER2-positive EBC females	12	20	94 [70/23/1]

EBC = early breast cancer; IV = intravenous; mod = moderate; SC = subcutaneous; sev = severe.

Safety Data from Study BP22023

The BP22023 protocol allowed healthy volunteers and patients to receive premedication (e.g., paracetamol and/or phenergan) prior to the administration of trastuzumab SC, at the discretion of the investigator, for prophylaxis of infusion-related reactions (IRRs).

In Part 1, a total of 86 AEs were observed in 27 out of 30 subjects. Of these, 71% were considered to be Grade 1 intensity, and 28% were Grade 2 intensity (Table 5). Two IRRs were observed in Cohort 1. One event was assessed as Grade 2 intensity, the other as Grade 3 intensity. Premedication to lower the risk of IRR was given to 2 subjects in Cohorts 1 and 3, respectively, and to one subject of Cohort 4. Neither of the healthy male volunteers experiencing an IRR in Cohort 1 had received any premedication before being administered trastuzumab IV. The number of subjects reporting AEs was similar in all the cohorts in Part 1, but there were fewer events reported in the SC cohorts. In Cohorts 3–5, in which male subjects received trastuzumab SC at 6, 8, and 10 mg/kg; there was no apparent dose-related increase in frequency or severity of AEs, and the SC administration was generally well tolerated.

In Part 2, a total of 181 AEs were observed in 39 out of 40 female patients. Of these, 72.5% were considered to be Grade 1 intensity, 25.5% were Grade 2 intensity, and there

were 4 (2%) Grade 3 AEs (Table 5). In Cohorts A and B, there was no apparent dose-related increase in the frequency or intensity of AEs observed, and the SC administration was generally well tolerated.

As this was the first study during which subjects received trastuzumab SC, special consideration was given to the local tolerability related to drug administration. In subjects who received trastuzumab SC, there were 18 AEs that were classified as administration site conditions. A total of 16 (89%) AEs were of mild intensity and included erythema (7), discoloration (5), injection-site swelling (2), injection-site discomfort (1), and injection-site reaction (1). There were two instances of moderate injection-site pain. There were no changes in laboratory parameters, vital signs or ECG parameters that constituted an AE.

Pharmacokinetic Data from Study BP22023

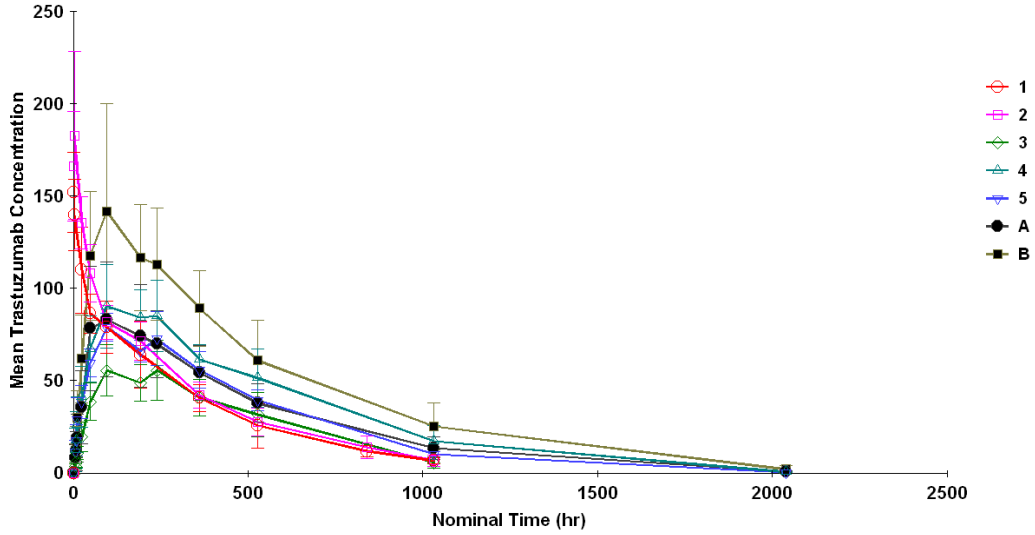
Comparable trastuzumab PK was observed in Part 1 between female patients and healthy male volunteers receiving 6 mg/kg IV, with a mean C_{max} of 185 µg/mL compared with 150 µg/mL and a mean AUC_{inf} of 1800 µg • day/mL compared with 1610 µg • day/mL in female patients and healthy male volunteers, respectively (Figure 1).

Mean maximum serum concentrations (C_{max}) of trastuzumab increased proportionally with increasing doses of trastuzumab SC, 66.8, 82.0, and 102 µg/mL for 6, 8, and 10 mg/kg trastuzumab SC, respectively. Mean $AUC_{0\text{-}inf}$ also increased over the range of SC doses administered, 1350, 1960, and 2500 day • µg/mL for 6, 8, and 10 mg/kg trastuzumab SC, respectively (Table 6).

Following preliminary PK analysis of trastuzumab serum samples in all subjects in Part 1 (Cohorts 1 to 5), 20 patients were administered a single dose of 8 mg/kg trastuzumab SC (**Cohort A**), as this was the trastuzumab SC dose level expected to achieve a comparable exposure to the approved maintenance dose of 6 mg/kg trastuzumab IV. In **Cohort B**, patients were administered a single dose of 12 mg/kg trastuzumab SC to assess PK characteristics and safety, as well as to support modelling and simulation. The absolute bioavailability based on $AUC_{0\text{-}inf}$ ranged between 83.9% and 93.2% in healthy male volunteers and 87.1% and 98.6% in female patients.

The available data suggested dose proportionality in C_{max} and $AUC_{0\text{-}inf}$ over the range of trastuzumab SC doses administered (6–12 mg/kg) both in Part 1 and Part 2.

Figure 1 Mean (±SD) Trastuzumab Concentration-Time Profile by Cohort



EBC = early breast cancer; IV = intravenous; SC = subcutaneous; SD = standard deviation.
1: 6 mg/kg IV, healthy subjects
2: 6 mg/kg IV, EBC subjects
3: 6 mg/kg SC, healthy subjects
4: 10 mg/kg SC, healthy subjects
5: 8 mg/kg SC, healthy subjects
A: 8 mg/kg SC, EBC subjects
B: 12 mg/kg SC, EBC subjects

Table 6 Mean (CV%) Trastuzumab Serum Pharmacokinetic Parameters, Following Trastuzumab IV and SC Administration, Study BP22023

Cohort	Route of Administration	Subjects (n)	Dose (mg/kg)	C_{max} (µg/mL)	t_{max} (hour) [a]	AUC_{inf} (day/µg/mL)	$t_{1/2}$ (hour)	C_{Day22} (µg/mL)
1	IV	H (6)	6	150 (9.57)	1.65 (1.6–24.0)	1610 (18.9)	254 (12.7)	25.6 (47.1)
2	IV	EBC (6)	6	185 (23.2)	3.00 (1.55–24.0)	1800 (13.9)	244 (28.4)	27.5 (27.1)
3	SC	H (6)	6	66.8 (17.1)	156.00 (95.95–216.10)	1350 (23.7)	227 (24.7)	31.6 (38.1)
5	SC	H (6)	8	82.0 (13.8)	96.00 (96.00–215.98)	1960 (12.4)	236 (18.6)	39.4 (13.9)
4	SC	H (6)	10	102 (16.8)	132.12 (96.00–216.00)	2500 (20.6)	240 (14.3)	51.4 (30.8)
A	SC	EBC (20)	8	88.4 (37.7)	97.13 (47.93–216.60)	2090 (30.6)	241 (19.9)	37.8 (27.5)
B	SC	EBC (20)	12	151 (38.7)	96.05 (24.53–241.40)	3550 (27.7)	270 (29.6)	60.8 (36.2)

AUC = area under the curve; C_{max} = maximum serum concentration; EBC = early breast cancer; H = Healthy; IV = Intravenous; SC = Subcutaneous; t_{max} = time to achieve maximum serum concentration; $t_{1/2}$ = elimination half-life.

Note: Values represent means (standard deviation), unless otherwise indicated.

[a] Median (min–max).

Plasma concentrations of rHuPH20 were assessed in all subjects who received trastuzumab SC at predose and 0.5 h, 1 h, and 24 h postdose. Plasma rHuPH20 concentrations were below the limit of quantification for all sampling points in all subjects, indicating that the use of the enzyme as a permeation enhancer for trastuzumab does not result in quantifiable systemic exposure to the enzyme.

Immunogenicity Results from Study BP22023

Blood samples were taken at screening, Days 15, 85 and follow-up (5 months postdose) to allow for testing of antibodies to either trastuzumab or rHuPH20.

Nine of 58 (15.5%) subjects who had been administered trastuzumab SC were deemed positive for antibodies to rHuPH20 after confirmatory assay analysis. Five of these subjects had a positive confirmatory assay at all timepoints including screening, one subject was positive at screening, Day 15 and follow up and negative at Day 85, one subject was positive at screening, Day 15 and Day 85 but negative at follow up, another one was positive at Day 85 but negative at follow-up; and the remaining subject was positive at Day 85 and follow-up. All samples were negative in the neutralizing antibody assay.

A total of 263 samples were assayed in 58 subjects for the occurrence of anti-trastuzumab antibodies. Eleven samples in 8 of 58 (14%) subjects receiving trastuzumab SC were positive for antibodies to trastuzumab after the confirmatory assay. All samples from the screening visits were negative for anti-trastuzumab antibodies. In 6 subjects out of the 8 above, the follow-up sample was negative after one positive sample. No anti-trastuzumab antibodies were detected in subjects receiving trastuzumab IV. Neutralizing antibody tests for trastuzumab were not performed, as the assay was not available at the time. Samples have been discarded in the interim. Likewise, results from titering assays are not available.

The presence of a positive confirmatory assay for trastuzumab or rHuPH20 was not associated with a difference in safety or trastuzumab PK profile. This also held true for the 3 patients who developed anti-drug antibodies (ADA) to both proteins.

Pharmacokinetic Modelling of Fixed Trastuzumab SC Dose Selection

In the dose-finding Study BP22023, subjects received trastuzumab SC on a body weight-adjusted basis. Preliminary trastuzumab IV and SC PK data from this study were integrated into a PK model, and simulations were then used to predict C_{trough} and AUC for various trastuzumab SC doses based on 100 simulations of 130 subjects, which provided a 5 to 95th% tile range for the 5th% tile, median, and 95% tile concentration values. The simulations were based on a normal distribution of body weight, with a mean of 68 kg and standard deviation of 11 kg. The simulations indicated that a flat and a weight-based dosing strategy would result in a comparable range of exposure with a relationship to body weight that is inverse, and a fixed dose of 600 mg would result in C_{trough} values that are at least as high as with the 3-weekly (Q3W) IV regimen (8 mg/kg loading dose followed by 6 mg/kg maintenance dose). For example, as shown in Table 7, the IV upper bound of the confidence interval (CI) of the median C_{trough} is 63 µg/mL and is comparable to the SC lower bound of the CI of the median C_{trough} predicted at 67 µg/mL.

Table 7 Predicted C_{trough} (µg/mL) at Pre-dose Cycle 8

	C_{trough} at Predose Cycle 8 (µg/mL)		
	5th% tile P5 [P5-P95]	Median [P5-P95]	95th% tile P95 [P5-P95]
Q3W IV regimen (8/6 mg/kg)	23 [16-32]	46 [37-63]	84 [67-109]
SC regimen 600 mg	38 [28-49]	79 [67-95]	143 [120-174]

P5 = 5th percentile; P95 = 95th percentile; Q3W = 3-weekly.

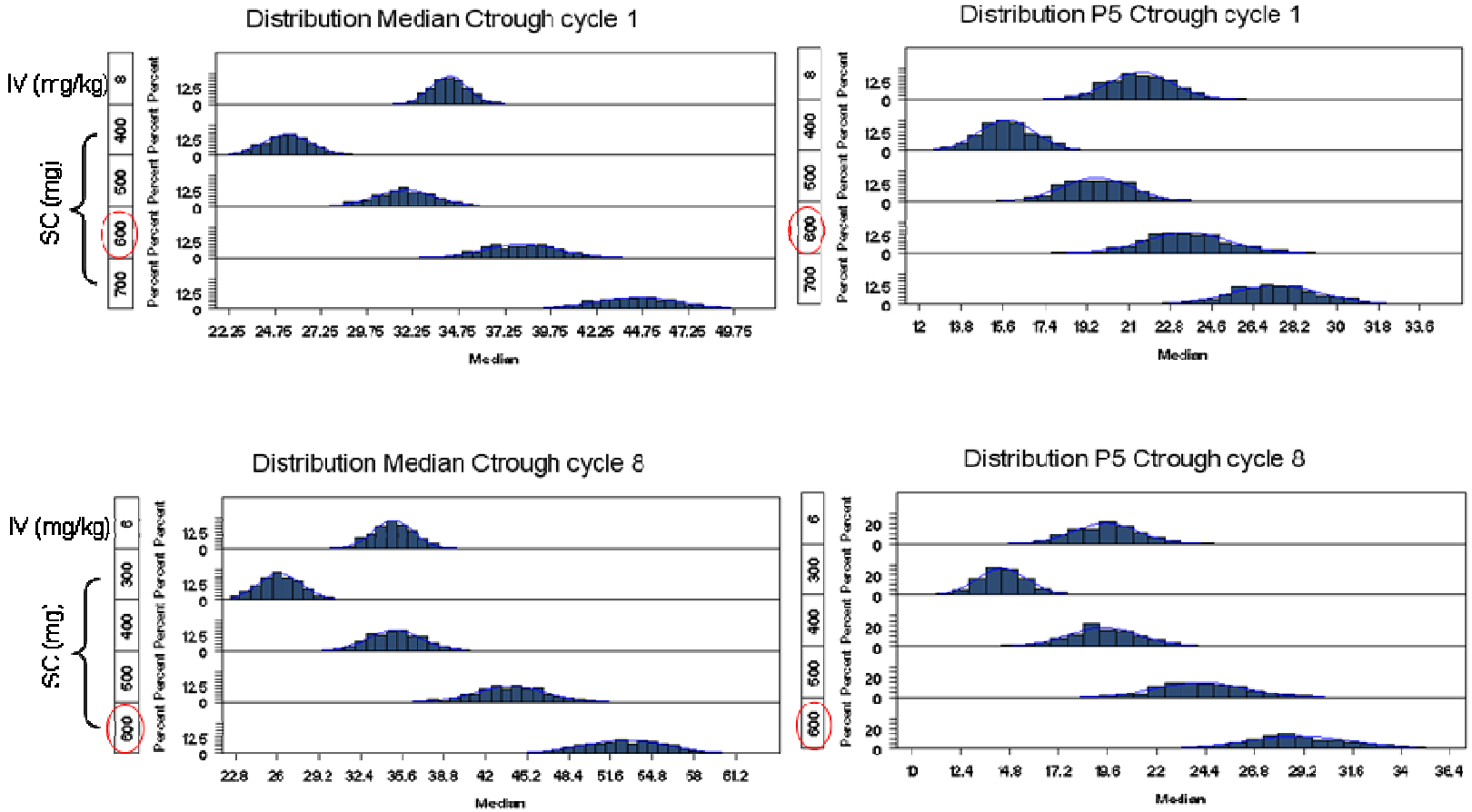
Figure 2 illustrates the distribution of predicted median C_{trough} and predicted 5th percentile of C_{trough}, respectively, at Cycles 1 and 8, comparing the IV loading and maintenance doses of 8 mg/kg and 6 mg/kg, and a fixed SC dose of 600 mg. For both

cycles, with the selected fixed dose of 600 mg, median C_{trough} values were predicted to be higher than those achieved with the IV doses.

Figure 3 illustrates the distribution of predicted median AUC_{tau} and predicted 5th percentile of AUC_{tau}, respectively, at Cycles 1 and 8, comparing the IV loading and maintenance doses of 8 mg/kg and 6 mg/kg and the fixed SC dose of 600 mg. For Cycle 8, with the selected fixed dose of 600 mg, median AUC_{tau} values were predicted to be higher than those achieved with the IV 6 mg/kg maintenance dose. For Cycle 1, median AUC_{tau} values were predicted to be lower than those achieved with the IV 8 mg/kg loading dose. It was predicted that with a 600 mg fixed dose of trastuzumab SC, a cumulative AUC comparable to the Q3W IV regimen would be reached during Cycle 3.

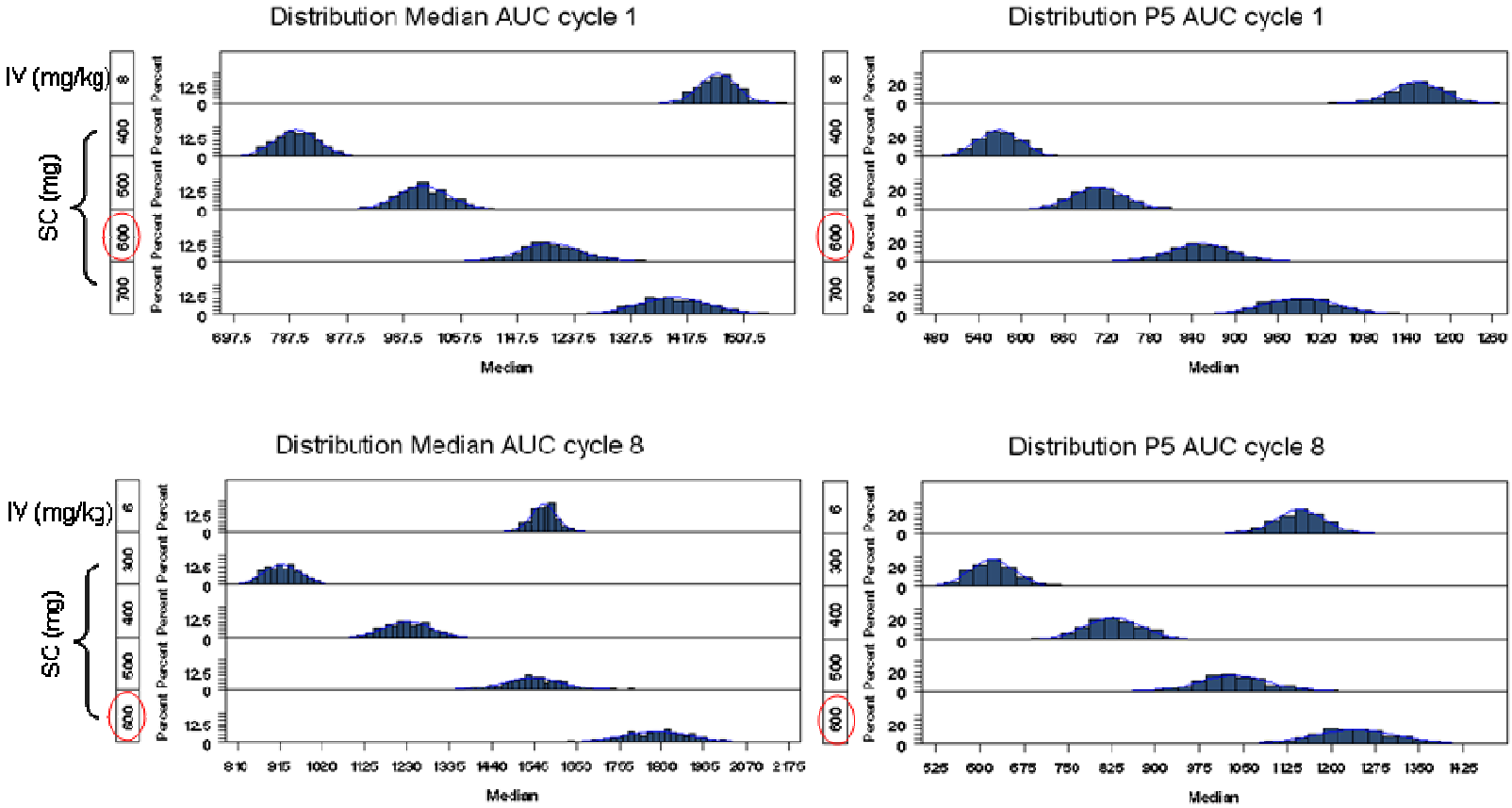
The predicted C_{max} values after SC administration (95th percentile) also did not exceed the maximum exposure previously measured for the IV regimen in the HERA trial (Clinical Study Report 1019820). Therefore, no unexpected safety issues related to trastuzumab exposure were anticipated with a 600 mg fixed dose of trastuzumab SC. Based on these data, a fixed dose of 600 mg was selected as an appropriate dose for further studies using trastuzumab SC.

Figure 2 Distribution or Simulated Median C_{trough} Levels at Cycles 1 and 8 with a Dose of 600 mg Trastuzumab SC



C_{trough} = trough plasma concentration; IV = intravenous; P5 = 5th percentile; SC = subcutaneous.

Figure 3 Distribution of Simulated Median AUC_{tau} Levels at Cycles 1 and 8 with a Dose of 600 mg Trastuzumab SC



AUC = area under the plasma concentration-time curve; IV = intravenous; P5 = 5th percentile; SC = subcutaneous.

1.2.2.3.2 Study BO22227 (HannaH)

The findings of Study BP22023 indicating that trastuzumab SC has a tendency toward fewer administration-related reactions compared to trastuzumab IV were further investigated in the Phase III clinical efficacy bridging Study BO22227 (HannaH).

Study BO22227 is a Phase III, randomized, open-label, multicenter trial involving 596 female patients with HER2-positive early breast cancer in which the pharmacokinetics, efficacy, and safety of trastuzumab SC were compared with IV trastuzumab. Co-primary endpoints are serum C_{trough} pre-surgery and pathological complete response (pCR).

In this study, patients with operable or locally advanced disease were randomized to eight cycles of either trastuzumab IV or trastuzumab SC given concurrently with chemotherapy. Patients randomized to trastuzumab IV received the standard 3-weekly regimen (8 mg/kg loading followed by 6 mg/kg every 3 weeks), and patients randomized to trastuzumab SC received a fixed dose of 600 mg of trastuzumab (formulated with rHuPH20 2000 IU/mL to give a fixed dose of 10,000 U) every 3 weeks by conventional SC injection using a syringe and needle. After surgery, patients received a further 10 cycles of trastuzumab IV or SC as per randomization to complete 1 year of treatment. Study BO22227 met its co-primary endpoints, which were the trastuzumab concentration in the blood (serum concentrations) and efficacy.

Results of the study indicated that trastuzumab SC demonstrated comparable efficacy to trastuzumab IV within the planned boundaries for non-inferiority with regard to the pCR and the concentration in the blood (C_{trough}). No new safety signals were identified with trastuzumab SC, and AEs were consistent with trastuzumab IV, with the most common AEs being infections and abnormal blood counts (anemia and low white blood cell count). The overall safety profile and tolerability in both arms was consistent with that expected from combination treatment with anthracycline, taxane, and trastuzumab. No new or unexpected safety findings were observed. The proportion of patients reporting an AE of any grade during neoadjuvant/adjuvant treatment and treatment-free follow-up was 93.9% (280 of 298 patients) in the trastuzumab IV arm compared with 97.3% (289 of 297 patients) in the trastuzumab SC arm. The most frequently occurring AEs were alopecia (62.8% in trastuzumab IV vs. 62.6% in trastuzumab SC), nausea (48.7% vs. 48.5%), neutropenia (46.3% vs. 44.1%), diarrhea (36.6% vs. 33.7%), asthenia (25.2% vs. 24.6), fatigue (26.5% vs. 22.6%), and vomiting (23.2% in each arm). Most AEs were Grade 1 or 2 in intensity. The incidence of Grade $\geq$3 events (severe) was 52% (155 of 298 patients) in the trastuzumab IV arm versus 51.9% (154 of 297 patients) in the trastuzumab SC arm. Full assessment of the data is publicly available (Ismael et al. 2012).

1.2.2.3.3 Study BO25532 (CP3)

Study BO25532 was a randomized, open-label, parallel, 2-arm, multicenter Phase I study to investigate the comparability of PK of trastuzumab administered subcutaneously

using either the SID or a conventional syringe with a hypodermic needle. The study also assessed the performance of the SID and evaluated the immunogenicity of trastuzumab and rHuPH20.

Enrollment was completed in September 2011, with a total of 119 healthy male subjects randomized 1:1 to receive a single 600 mg SC injection by either administration method. The primary objective of the study was met, with the results for both co-primary PK endpoints within the standard bioequivalence range of [0.8, 1.25], meeting the pre-specified criteria for comparability. Sensitivity analyses of the co-primary endpoints that included nondose normalized or non-body weight-adjusted calculations, were in line with the primary analysis.

Trastuzumab was well tolerated after single-dose administration by both methods, and there were no apparent differences related to the injection method (Wynne et al. 2012).

1.2.2.3.4 Study MO22982 (PrefHer)

This is a Phase II international, randomized, open-label, two-cohort, two-arm crossover study to evaluate patient's preference and HCP satisfaction with SC versus IV administration of trastuzumab in HER2-positive EBC following surgery and completion of chemotherapy (neoadjuvant or adjuvant). Approximately 200 patients will be randomized 1:1 in each cohort to receive either trastuzumab treatment. In Cohort 1, half of the patients will receive trastuzumab SC (600 mg fixed dose; 4 cycles) via a single use injection device (SID) followed by trastuzumab IV (8 mg/kg loading dose required only if Cycle 1 of study treatment is the initial dose of trastuzumab, otherwise 6 mg/kg Q3W; 4 cycles) or to trastuzumab IV followed by trastuzumab SC. All patients will then continue to receive the remaining trastuzumab IV to complete 18 cycles of trastuzumab administration. In Cohort 2, half of the patients will receive trastuzumab SC (600 mg fixed dose; 4 cycles) administered from a vial with a hand-held syringe followed by trastuzumab IV (8 mg/kg loading dose required only if Cycle 1 of study treatment is the initial dose of trastuzumab, otherwise 6 mg/kg Q3W; 4 cycles) or to trastuzumab IV followed by trastuzumab SC. All patients will then continue to receive the remaining trastuzumab SC to complete 18 cycles of trastuzumab administration. The primary endpoint is the proportion of subjects indicating an overall preference for either the SC or the IV route of administration. Efficacy endpoints include EFS. Immunogenicity of trastuzumab and rHuPH20 will also be evaluated.

1.2.3 Subcutaneous Single-Use Injection Device (SID)

The SID is a single-use device for the subcutaneous administration of medicinal products such as trastuzumab SC. The medicinal product to be injected is contained in an integral non-removable cartridge. The entire content of the cartridge is delivered to the patient in a single injection through a needle that retracts when the injection is complete and if prematurely removed from the body to prevent needle stick injuries in handling. The administration rate is fixed (approximately 1 mL/min, resulting in an approximate 5-minute injection time), and the dosage delivered is preset and controlled

at the product manufacturing stage (i.e., 600 mg of trastuzumab formulated with 10,000 U of rHuPH20). The medicinal product is administered through intact skin into the patient's upper thigh.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Patients with HER2-positive early breast cancer frequently require extensive treatment lasting months or years. Many require surgery, adjuvant chemotherapy (usually given IV for 4–6 months) and/or hormonal therapy, and radiotherapy (often given daily for 4–6 weeks), as well as trastuzumab. Adjuvant trastuzumab is given IV q1w or Q3W for a total of one year. This necessitates regular clinic visits, and, when started after completion of adjuvant chemotherapy and adjuvant radiotherapy if indicated, it greatly extends the period of time over which the patient is obliged to attend the hospital or clinic, which can cause inconvenience and increased costs to patients. Even when started concurrently with the taxane component of chemotherapy (Herceptin license permitting), trastuzumab monotherapy still continues for several months after completion of other systemic therapy.

Trastuzumab infusions are given over 30–90 minutes (or longer if there are infusion-related symptoms). SC administration of trastuzumab is quicker (lasting up to 5 minutes), and this alone could improve convenience for patients (and clinic staff). Furthermore, SC administration does not require IV access (which can be problematic in some patients after completion of chemotherapy). Use of a SID may also enable self-administration of trastuzumab in the future. This could potentially further improve convenience for patients and compliance with therapy.

The most clinically relevant AE associated with trastuzumab IV is left ventricular cardiac dysfunction or CHF. Cardiac toxicity, as measured by the rate of NYHA Class III/IV CHF was the most significant AE, occurring in 0%–3.8% of patients in the trastuzumab-containing arms of six randomized adjuvant trials (see Section 1.2.1.2). The current study is designed to investigate the safety and tolerability of two SC administration methods for trastuzumab in the (neo-)adjuvant setting, i.e. assisted administration using a conventional syringe (vial formulation) and self-administration using a SID. The observed incidence of CHF-related SAEs served as basis for the determining the sample size for the current trial. Patient satisfaction with self-administration using a SID is assessed as part of the secondary objectives of the study.

Trastuzumab is now a standard component of (neo)-adjuvant treatment in patients with HER2-positive EBC. The trastuzumab SC dose selected for this study is consistent with the findings of the BP22023 (CP2) trial and identical to that evaluated in the BO22227 (HannaH) study (see Section 1.2.2 for details). Efficacy is hence expected to be comparable to that that observed in trastuzumab IV trials. Safety data from the BP22023 and BO22227 studies show that trastuzumab SC is well tolerated, with no safety signals detected compared to trastuzumab IV in the BO22227 study. The benefit

to risk ratio of adjuvant trastuzumab SC in the current trial is therefore expected to be favorable. Further, the convenience of SC administration of trastuzumab will give patients greater independence, which is expected to increase compliance.

One of the exploratory objectives of the study is to collect additional safety data over a specified observation time (according to trastuzumab EU SmPc) following trastuzumab administrations in patients using the SID (**Cohort B**).

It will be assessed whether the prolonged observation time of the patients following trastuzumab SC administration (during the pre-specified time as per SmPC) is required for patients' safety. It is anticipated there may be a higher possibility of AEs following the first administration of trastuzumab; therefore, the patient will be required to remain at site for 6 hours after start of the first trastuzumab administration. For all subsequent trastuzumab applications, patients will be required to remain onsite for 2 hours after start of drug administration. However, the patient may be required to remain onsite for an extended period of time if considered clinically necessary by the investigator. During this time, detailed information of AEs and associated treatment will be recorded and analyzed relative to the last preceding administration of trastuzumab.

Therefore, in **Cohort B**, in addition to onset and resolution dates and times of AEs, detailed information about premedications prior to trastuzumab administration will be collected. Also, in addition to the date, the onset and resolution time of the treatment of AEs occurring during the observation time will be investigated. At the discretion of the investigator, patients will have the opportunity to self-administer trastuzumab via the SID; therefore, the SID performance under self-administration conditions will be monitored.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of the study is to assess the overall safety and tolerability of trastuzumab SC in HER2-positive EBC patients with assisted administration using a conventional syringe and needle (vial formulation) or with assisted- and self-administration using a SID in selected patients.

2.2 SECONDARY OBJECTIVES

Secondary objectives include the evaluation of the following parameters:

- Efficacy (both cohorts):
  - DFS (Disease-free survival)
  - OS (Overall survival)
- Patient satisfaction with trastuzumab SC administration using the SID (patients in **Cohort B** who went on to self-administration of the study drug).

2.3 EXPLORATORY OBJECTIVES

Additional, exploratory objectives will be investigated in a subset of patients (**Cohort B**) at selected study sites:

1. To assess the immunogenicity of trastuzumab and recombinant human hyaluronidase (rHuPH20)
2. To examine and characterize tolerability of the trastuzumab SC over a 6-hour time period after the start of the first administration and over a 2-hour time period after the start of subsequent trastuzumab administrations (only in patients using the SID [**Cohort B**])
3. Monitoring of SID usability in a subgroup of 48 patients in **Cohort B**

In addition, in some countries and sites, medical care utilization (MCU; e.g., time and motion) and/or pharmacoeconomic substudies will be conducted. Details of the substudies will be described in separate protocols.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a Phase III, prospective, two-cohort, non-randomized, multicenter, multinational, open-label study in approximately 2500 patients with HER2-positive EBC who are eligible for anti-HER2 therapy. A planned total of approximately 2500 evaluable patients will be enrolled into the study. The trial will be conducted at approximately 520 centers in approximately 60 countries.

All potential study patients must provide signed written informed consent (approved by the relevant independent ethics committee [EC]) before undergoing any study-specific procedure. Results of the screening assessments must be available, and patients must meet all eligibility criteria prior to enrollment into the study.

Eligible patients will be allocated to **Cohort A** or **B** at the investigator's discretion depending upon availability of the cohorts for recruitment:

- **Cohort A** (approximately 1800 patients): trastuzumab SC 600 mg assisted administration into the thigh over a period of approximately 5 minutes using conventional handheld syringes with hypodermic needles
- **Cohort B** (approximately 700 patients): trastuzumab SC at a fixed dose of 600 mg presented in a SID. The first administration will be assisted (performed by a HCP). If well tolerated and if the patient is willing and judged competent by the HCP to do so, subsequent administrations may be self-administered into the thigh over a period of approximately 5 minutes using the SID for a total of up to 18 cycles (3-weekly).

  Patients will remain at the study site to be observed for a period of 6 hours after their first trastuzumab administration and 2 hours thereafter for subsequent

trastuzumab administrations. Patients may be required to remain onsite for an extended period of time if considered clinically necessary by the investigator.

To allow for the enrollment of 1800 patients in **Cohort A** (compared to 700 patients in **Cohort B**), recruitment for **Cohort A** may be initiated earlier than recruitment for **Cohort B**.

The study design is shown in Figure 4.

Patients in both cohorts will receive a fixed dose of 600 mg trastuzumab SC throughout the study, administered 3-weekly for a total of 18 cycles, unless disease recurrence, unacceptable toxicity, or patient withdrawal necessitates earlier treatment cessation. All study treatment administrations in both cohorts will occur in a hospital setting.

Trastuzumab SC treatment may be initiated:

- After completion of neoadjuvant or adjuvant chemotherapy (sequentially)
- In combination with neoadjuvant or adjuvant paclitaxel or docetaxel chemotherapy (concurrently)
- or without adjuvant chemotherapy
- or in combination with neoadjuvant chemotherapy followed by trastuzumab therapy for locally advanced (including inflammatory) disease or tumors >2 cm in diameter

For patients receiving trastuzumab SC with concurrent chemotherapy, trastuzumab SC must be administered first, followed by the administration of chemotherapy as per standard site procedures. The observation time starts with the start of trastuzumab SC administration.

The enrollment of patients treated without neoadjuvant or adjuvant chemotherapy, such as:

- Patients with low risk node negative tumors ≤ 1.0 cm
- Elderly patients (>65 years of age)
- or patients who refuse chemotherapy will be limited to $\leq 10\%$ of the total study population)

Hormonal therapy and radiotherapy (if applicable) may be given concomitantly with trastuzumab SC, as per local guidelines.

Patients will be assessed for safety and efficacy, as detailed in Appendix 1, Schedule of Assessments. In addition to efficacy and safety assessments, select sites will also perform immunogenicity testing to determine whether HAHAs against trastuzumab or rHuPH20 develop in patients receiving trastuzumab SC using the SID. Since the evaluation of anti-trastuzumab assay results requires corresponding serum trastuzumab concentrations, the anti-trastuzumab analyses will be coupled with PK assessments.

Patients in either study arm who cannot tolerate trastuzumab SC will come off study and further treated at the investigator's discretion.

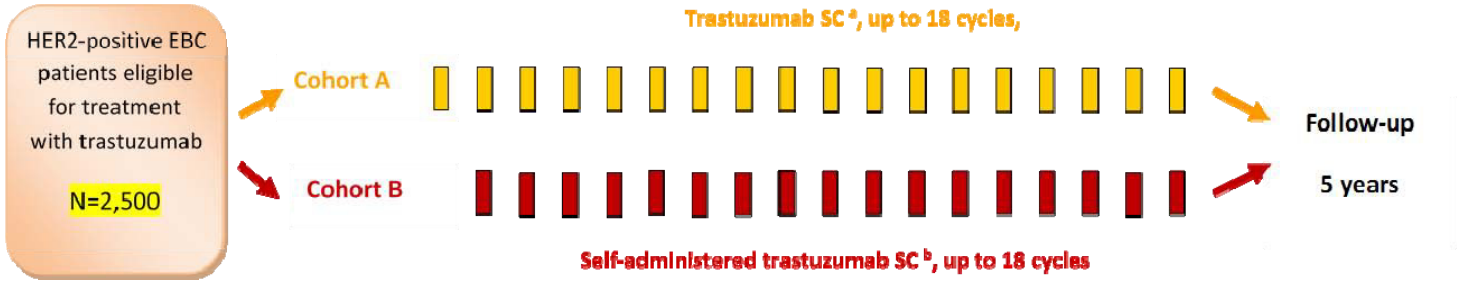
Patients will undergo a Safety Follow-up visit 4 weeks after their last dose of study treatment, with further follow-up according to the American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006) *or investigator's routine practice.* All patients will be followed-up for cancer recurrence and survival until study end. The duration of follow-up will be at least 5 years after their last study treatment, unless one of the following occurs first: withdrawal of consent, loss to follow-up, or death. After disease progression, patients will be managed as per local practice and followed for survival only.

In some countries and sites, MCU (e.g., time and motion) and/or pharmacoeconomic substudies will be conducted. Details of the substudies will be described in separate protocols.

The primary analysis of safety endpoints and a preliminary analysis of efficacy (DFS and OS) will take place when all patients have received 18 cycles of trastuzumab SC and have completed the post-treatment Safety Follow-up assessments. The final analysis of OS and DFS and updated summaries for safety parameters will be performed when the last patient has been followed up for at least 5 years after her/his last study treatment, or earlier, if one of the following is documented for all treated patients: withdrawal of consent, loss to follow-up, or death. This is expected to take place approximately 8 years after the enrollment of the first patient, based on an expected 18-month recruitment period per cohort, 12 months of study treatment, and 5 years of follow-up after the last study treatment. The study design is shown in Figure 4 and the Schedule of Assessments in Appendix 1.

3.1.1 Overview

Figure 4 Study Design



EBC = early breast cancer; HCP = healthcare provider; HER2 = human epidermal growth factor receptor-2; SC = subcutaneous; SID = single-use injection device.

Notes: Participating investigators must opt for one route of administration per patient. For enrollment to **Cohort B**, patients need to be willing to self-administer the study drug based on the instructions for use supplied with the SID and personal instructions provided by an HCP during the first assisted administration. All trastuzumab SC administrations will occur in a hospital setting. Patients in both cohorts will receive trastuzumab SC 3-weekly, for a total of 18 cycles, unless disease recurrence, unacceptable toxicity or patient withdrawal necessitates early cessation of treatment. If trastuzumab SC is initiated in the neoadjuvant phase, surgery should be programmed after the dosing at Cycle 8, without interruption of trastuzumab treatment.

[a] **Cohort A**: Trastuzumab SC 600 mg will be injected by an HCP into the thigh over a period of approximately 5 minutes using a conventional handheld syringe with a gauge 25 or 27 hypodermic needle.

[b] **Cohort B**: Trastuzumab SC 600 mg will be injected into the thigh over a period of approximately 5 minutes using the SID. The first injection will be administered by a trained HCP (physician or nurse). Patients assessed by the investigator as competent to self-administer the study drug using the SID and are willing to will be allowed to self-administer the remaining trastuzumab SC doses under the direct supervision of a HCP. Patients not deemed competent to self-administer the study drug, or are not willing will have all their trastuzumab SC doses administered by a trained HCP (physician or nurse).

3.1.2 Steering Committee

A Steering Committee is established to provide scientific oversight and to ensure that the risk-benefit assessment is maintained during the total duration of the trial. Responsibilities of the Steering Committee include recommendation to the Sponsor of any protocol amendments, monitoring of accrual, compliance and safety during the conduct of the trial, and reviewing the results of three interim safety analyses when approximately 500, 1000, and 2500 patients have received at least one trastuzumab SC injection. Upon study completion, the Steering Committee will provide its interpretation of the results to the Sponsor, including their proposal for publications. Timing and type of publications generated by the SafeHer study will be defined in conjunction with the Sponsor.

The SafeHer Steering Committee is made up of investigators and Roche representatives and meets at regular intervals. The committee is composed of up to 10 members, including the Chairperson. The Chairperson of the Steering Committee is responsible for scheduling and conducting the meetings. Decisions of the Steering Committee are based on a majority vote.

Refer to the SafeHer Steering Committee Charter for further details.

3.2 END OF STUDY

End of study is defined as the last patient last visit in the follow-up period. The study will end when all patients have been followed for approximately 5 years after their last study treatment, or earlier, if one of the following is documented for all treated patients: withdrawal of consent, loss to follow-up, or death. The final analysis of OS and DFS and updated summaries for safety parameters will be performed at this stage.

The study is estimated to last approximately 8 years.

3.3 RATIONALE FOR STUDY DESIGN

This Phase III prospective, two-cohort non-randomized, multicenter, multinational, open-label study will assess the overall safety and tolerability of two SC administration methods of trastuzumab (assisted administration using a conventional needle and syringe and self-administration using a SID) in HER2-positive EBC patients. The safety and tolerability of the two SC administration methods will be evaluated over a standard treatment period of 18 cycles (administered every 3 weeks). With this comprehensive approach, any potential problems associated with multiple administrations (e.g., positioning the SID to avoid previous sites of administration) will also be assessed.

Patients will be allocated to **Cohort A** or **B** at the investigator's discretion. For enrollment into **Cohort B**, patients need to be willing to self-administer the study drug from the SID based on personal instructions/training provided by an HCP during the first assisted administration in addition to a quick reference guide and an instructional

animation describing the injection device handling and use, including how to respond if the SID loses sufficient contact with the body.

Administration by the SID could enable self-administration of trastuzumab in the future. The SID satisfaction questionnaire used in this study and the device usability monitoring questionnaire has been developed specifically for this purpose.

3.3.1 Rationale for Test Product Dosage

Subcutaneous trastuzumab will be given Q3W at a fixed dose of 600 mg in both cohorts. Use of a fixed dose for all patients and all cycles greatly simplifies dosing, reduces the potential for error, and reduces wastage. Fixed doses have been used for other therapeutic monoclonal antibodies, particularly in chronic conditions, such as rheumatoid arthritis (e.g., adalimumab). The fixed dose of trastuzumab for SC administration was selected with the aim of achieving trastuzumab serum trough concentrations (C_{trough}) that are non-inferior to those obtained with Q3W trastuzumab IV administration. The fixed (600 mg) dose of trastuzumab used in this study was calculated based on PK modelling of preliminary data from the BP22023 study (see Section 1.2.2.3.1), which showed that 600 mg doses of trastuzumab SC were able to achieve serum C_{trough} levels at least as high as those achieved with standard weight-adjusted trastuzumab IV dosing. Trastuzumab exhibits linear pharmacokinetics in the clinical dose range, which is an indication that target receptors are saturated. Therefore, achieving C_{trough} levels with SC administration that are at least as high as with the IV dosing, indicates that efficacy should be comparable. Patients with lower body weight may be exposed to higher C_{trough} levels than if they were dosed on a weight-adjusted basis. However, studies in which higher than standard (or more frequent) doses of trastuzumab were given (Clinical Study Report 1026709; Vogel et al. 2002) and reports of patients accidentally overdosed with trastuzumab IV do not indicate any detrimental effect on patient safety. Moreover, based on data from the BP22023 study, the predicted maximal concentrations following eight Q3W cycles of 600 mg are expected to be below the C_{max} of trastuzumab IV observed in the MO16982 study (range 199–375 mg/L). In Study MO16982, patients were initially dosed with 6 mg/kg weekly, and no increase in AEs was observed (Clinical Study Report 1026709). More recently, results of the HannaH study (BO22227) have been released. The study met its two co-primary endpoints, i.e. observed trastuzumab C_{trough} after 7 cycles and the primary efficacy variable of pathological complete response, thereby demonstrating comparable bioavailability and efficacy of the SC and IV formulations of trastuzumab.

The fixed dose of 600 mg of trastuzumab SC will be administered with a fixed dose of 10,000 U of rHuPH20 (2000 U/mL). The dose of rHuPH20 was selected based on nonclinical PK studies with a number of antibodies, including trastuzumab. These studies showed a trend for increasing dispersion and absorption with increasing concentrations of rHuPH20 (Clinical Study Report 1029906; Halozyme Study Report 09520). Of note, a higher amount of rHuPH20 (6000 U/mL) did not improve the

absorption of trastuzumab as compared to a formulation containing 2000 U/mL rHuPH20. The selected rHuPH20 concentration was further verified in clinical studies for satisfactory absorption parameters. Nonclinical and clinical data demonstrate that the selected amount of rHuPH20 contained in the trastuzumab SC formulation is well tolerated.

3.3.2 Rationale for the Patient Population

Adjuvant systemic therapies for early breast cancer have contributed to the substantial decline in breast cancer mortality in the past couple of decades (Verma et al. 2010; Colozza et al. 2006). The introduction of trastuzumab has particularly improved the outcome for early breast cancer patients with HER2-positive disease. Since its initial approval in 1998, trastuzumab has become standard of care for patients with HER2-positive breast cancer and is widely used for its approved indications in both the adjuvant and metastatic settings (Ross et al. 2009; NCCN 2010; Gnant et al. 2011; Aebi et al. 2011).

HER2 positivity, defined as the over-expression or amplification of HER2, is a prerequisite for the use of trastuzumab. Recent reports indicate that approximately 15%–20% of breast cancers are HER2-positive (Ross et al. 2009; Lund et al. 2010). Patients with HER2-positive early breast cancer frequently require extensive treatment lasting months or years. Many require surgery, adjuvant chemotherapy (usually given intravenously for 4–6 months) and/or hormonal therapy (given for 5–7 years), and radiotherapy (often given daily for 4–6 weeks), as well as trastuzumab. Adjuvant trastuzumab is given IV every week or every three weeks for a total of one year.

Although trastuzumab in combination with chemotherapy is now standard of care for patients with HER2-positive EBC larger than 1 cm, its role in the management of small (≤1 cm) HER2-positive tumors has not been established. There are two main reasons for this gap: first of all, most small breast cancers have a good prognosis and adjuvant chemotherapy is not routinely recommended for their management. In addition, due to this perceived good prognosis, patients with small (<1 cm, T1a,b) node-negative (N0) HER2-positive cancers were largely excluded from the pivotal adjuvant trastuzumab trials (Constantinidou and Smith 2011). However, recent data from several retrospective analyses suggest that small HER2-positive cancers might have a worse clinical outcome than previously estimated, and that more active adjuvant treatment including anti-HER2 therapy may be warranted in these cases (Amar et al. 2010; Tanaka et al. 2011; Constantinidou and Smith 2011). Subset analysis of one trastuzumab trial (HERA) demonstrated that patients with 1–2 cm cancers derived at least as much clinical benefit from 1 year of adjuvant trastuzumab with chemotherapy as the overall cohort (Piccart et al. 2005; Smith et al. 2007; Untch et al. 2008), and 2 retrospective studies have confirmed the same observation (McArthur et al. 2009; Rodrigues et al. 2010). These findings raise a key, but currently unanswered, clinical question of whether patients with small HER2-positive cancers should be offered adjuvant trastuzumab and

chemotherapy (Banerjee and Smith 2010; Constantinidou and Smith 2011). The importance of this issue is underscored by the steady increase in the number of women being diagnosed with T1a,bN0 primary tumors, which is largely due to the introduction of mammography screening programs and increased breast cancer awareness (Banerjee and Smith 2010; Fracheboud et al. 2004).

In addition to patients with small HER2-positive tumors, there are other relevant subpopulations with HER2-positive EBC who do not receive adjuvant chemotherapy. These include elderly patients and patients refuse chemotherapy due to the associated toxicities. Elderly patients with hormone-sensitive HER2-positive EBC may show benefit from endocrine treatment in combination with trastuzumab only (Constantinidou and Smith 2011).

In the current study, patients with HER2-positive EBC treated without neoadjuvant or adjuvant chemotherapy (such as patients with low-risk node-negative tumors $\leq$1.0 cm, elderly patients [$>$65 years of age], or patients who refuse chemotherapy) will comprise approximately 10% of the overall study population. Importantly, a prospectively planned subgroup analysis is expected to produce relevant data on the efficacy and safety of trastuzumab SC in this important subset of patients.

3.3.3 Rationale for Control Group

Not applicable; no formal statistical comparison of **Cohort A** and **Cohort B** is planned.

3.3.4 Rationale for Immunogenicity and Pharmacokinetic Assessments

With the introduction of a SC administration route, there is a potential that the previously observed very low incidence of HAHA formation (1 of 903 patients in previous clinical trials) could be increased. Based on published studies comparing IV and SC administration of protein drugs, there were either no significant increases in the incidence of HAHA following SC administration, or, in cases where increased immunogenicity was observed, the magnitude of the increase was small, i.e. less than 2-fold (Hale et al. 2004; Srinivas et al. 1997).

Immunogenicity testing is included in this study to determine whether HAHAs against trastuzumab or rHuPH20 develop, and whether these affect the safety and/or efficacy of trastuzumab SC. Samples for immunogenicity testing will be collected from a subset of patients enrolled in **Cohort B** at select sites (see Section 3.4.4).

3.3.5 Rationale for Observation Time Assessments

One of the exploratory objectives of the study is to collect additional safety data over a specified observation time (according to trastuzumab EU SmPC) following trastuzumab administrations in patients using the SID (**Cohort B**).

It will be assessed whether the prolonged observation time of the patients following trastuzumab SC administration (during the pre-specified time as per SmPC) is required for patients' safety. It is anticipated there may be a higher possibility of AEs following the first administration of trastuzumab. Therefore, the patient will be required to remain at site for 6 hours after start of the first trastuzumab administration. For all subsequent trastuzumab applications, patients will be required to remain onsite for 2 hours after start of drug administration. However, the patient may be required to remain onsite for an extended period of time if considered clinically necessary by the investigator. During this time, detailed information on AEs and associated treatment will be recorded and analyzed relative to the last preceding administration of trastuzumab.

Therefore, in **Cohort B**, in addition to onset and resolution dates and times of AEs, detailed information about premedications prior to trastuzumab administration will be collected. Also, in addition to the date, the onset and resolution time of the treatment of AEs occurring during the observation time will be investigated. At the discretion of the investigator, patients will have the opportunity to self-administer trastuzumab via the SID; therefore, the SID performance under self-administration conditions will be monitored.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures will be analyzed as secondary endpoints in this study and are defined as follows:

- DFS: time from the date of first treatment to the date of local, regional or distant recurrence, contralateral breast cancer or death due to any cause. The DFS rate at 2 years and yearly up to 5 years will also be presented.
- OS: time from the date of first treatment until date of death, regardless of the cause of death. The OS rate at 2 years and yearly up to 5 years will also be presented.

Patients in **Cohort B**, who went on to self-administration of the study drug will be asked to rate their overall satisfaction with trastuzumab SC administrations using the SID by completing a 5-item SID satisfaction questionnaire. The questionnaire will be completed after the 4th cycle and at the Safety Follow-up visit (or at least 1 day after the last trastuzumab SC injection), after a minimum of 2 successful self-administrations of the study drug.

The SID satisfaction questionnaire was created specifically for this trial (see Appendix 6).

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- All clinical adverse events (AEs) and serious adverse events (SAEs), as well as abnormal laboratory values, will be recorded and graded according to the National

Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0.

- Cardiac function will be evaluated by measuring left ventricular ejection fraction (LVEF) (using echocardiography, Multi Gated Acquisition (MUGA) scan or Magnetic Resonance Imaging [MRI]) and ECG. Symptomatic left ventricular dysfunction (CHF) will be graded according to NCI-CTCAE, version 4.0 and the NYHA functional classification.
- All concomitant medication will be recorded between the Screening and the Safety Follow-up visits. Thereafter, breast cancer treatments (e.g., endocrine therapy), anti-cancer treatments given to treat a recurrence, and medications related to the treatment of SAEs *will be recorded*.

3.4.3 Patient-Reported Outcome Measures

Not applicable.

3.4.4 Exploratory Outcome Measures

Immunogenicity of trastuzumab and rHuPH20 will be tested in a subset of patients enrolled in **Cohort B** at select sites. Serum samples (for anti-trastuzumab antibody analysis) and plasma samples (for anti-rHuPH20 antibody analysis) will be drawn at baseline (after eligibility is confirmed, i.e., just before the first study treatment), on-treatment (pre-Cycle 9 dose, Week 25), and at least 6 months after the end of treatment for testing in a central laboratory.

In addition to the study assessments described in Appendix 1, all clinical AEs that occur during the observation period will be collected for all patients in **Cohort B** (within 6 hours after start of the first trastuzumab administration or within 2 hours after start of following trastuzumab administrations). Data collected during the observation period will include: frequency, incidence, and grade of AEs; onset and resolution times of AEs (dd:mm:yyyy:hh:mm); outcome of AE; and details of treatments provided following AEs during the observation period.

Information on the usability of the SID will be collected via SID monitoring questionnaire (Appendix 7), will be provided to the first 48 patients enrolled in **Cohort B** who were judged able and were willing to self-administer remaining doses from the SID under direct observation of the HCP. The SID Device Observation is to be completed by HCPs.

The exploratory MCU and/or pharmacoeconomic parameters will be described in separate substudy protocols.

4. MATERIALS AND METHODS

4.1 PATIENTS

The study will recruit adult consenting patients with newly diagnosed HER2-positive (IHC 3+ or HER2-positive in situ hybridization [ISH]) early breast cancer who are eligible for treatment with trastuzumab (e.g., clinical Stage I [T1, N0, M0] to IIIC [any T, N3, M0]). Patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low-risk node-negative tumors $\leq$1.0 cm, elderly patients ($>$65 years of age), or patients who refuse chemotherapy, will also be eligible to participate in the study, but their enrollment will be limited to approximately $\leq$10% of the total study population.

Under no circumstances are patients who enroll in this study permitted to be re-enrolled to the same study for a second course of treatment.

4.1.1 Inclusion Criteria

Patients must meet ALL of the following criteria to be eligible for participation in this study according to the timing specified in the schedule of assessment:

1. Signed written informed consent approved by the reviewing independent Ethics Committee (EC)
2. Female or male aged 18 years or above
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
4. Histologically confirmed early invasive HER2-positive carcinoma of the breast with no evidence of residual, locally recurrent, or metastatic disease and defined as clinical Stage I (T1, N0, M0) to IIIC (any T, N3, M0) that is eligible for treatment with trastuzumab

   Note: Patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low-risk node-negative tumors $\leq$1.0 cm, elderly patients ($>$65 years of age), or patients with HER2-positive EBC but denying chemotherapy, will also be eligible to participate in the study, but their enrollment will be limited to approximately $\leq$10% of the total study population.
5. HER2-positive EBC, defined as IHC 3+ or positive in situ hybridization (ISH testing) by validated and approved methods within a certified laboratory
6. Screening left ventricular ejection fraction (LVEF) $\geq$55% as measured by echocardiography, multi-gated acquisition (MUGA) scan, or Magnetic Resonance Imaging (MRI) per local practice
7. Agreement to use an adequate, nonhormonal means of contraception by women of childbearing potential (defined as premenopausal and not surgically sterilized or $<$1 year after the onset of menopause) and by male participants with partners of childbearing potential only. Examples of adequate contraceptive measures are an intrauterine device, a barrier method (condoms or diaphragm) in conjunction with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are not acceptable for females participating in the study.

8. Intact skin at site of SC injection on the thigh

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible for participation in this study:

Cancer-related Criteria:

1. Previous neoadjuvant or adjuvant breast cancer treatment with an approved or investigational anti-HER2 agent
2. History of other malignancy which could affect compliance with the protocol or interpretation of results (including previous invasive ipsilateral or contralateral breast cancer). Patients with curatively-treated carcinoma in situ of the cervix or basal cell carcinoma and patients with other curatively-treated malignancies other than breast cancer who have been disease-free for at least 5 years are eligible.
3. Past history of ductal carcinoma in situ (DCIS) within the last 5 years that has been treated with any systemic therapy OR with radiation therapy to the ipsilateral breast where invasive cancer subsequently develops. Patients who had their DCIS treated with surgery only are allowed to enter the study.
4. Metastatic disease

Hematological, Biochemical, and Organ Function:

5. Inadequate bone marrow function (as indicated by any of the following):
   - Total white blood cell count (WBC) $< 2500/mm^3$ ($< 2.5 \times 10^9/L$)
   - Neutrophil count $< 1500/mm^3$ ($< 1.5 \times 10^9/L$)
   - Platelets $< 100{,}000/mm^3$ ($< 100 \times 10^9/L$)
   - Hemoglobin < 10 g/dL
6. Impaired hepatic function (as indicated by any of the following):
   - Serum total bilirubin $> 1.5 \times$ upper limit of normal (ULN)
   - Alanine amino transferase (ALT) $> 2.5 \times$ ULN
   - Aspartate amino transferase (AST) $> 2.5 \times$ ULN
   - Alkaline phosphatase (ALP) $> 2.5 \times$ ULN
7. Impaired renal function, as indicated by serum creatinine $> 1.5 \times$ ULN

Other Study Drug-related Exclusion Criteria:

8. Serious cardiac illness or medical conditions including but not confined to:
   - History of documented heart failure or systolic dysfunction (LVEF $< 50\%$)
   - High-risk uncontrolled arrhythmias such as atrial tachycardia with a heart rate > 100/min at rest, significant ventricular arrhythmia (ventricular tachycardia), or higher-grade atrioventricular (AV) block (second-degree AV block Type 2 [Mobitz 2] or third-degree AV block)

- Angina pectoris requiring anti-anginal medication
- Clinically significant valvular heart disease
- Evidence of transmural infarction on electrocardiogram (ECG)
- Poorly controlled or uncontrolled hypertension (blood pressure consistently over 140/90 mmHg, despite treatment) or history of hypertensive crisis or hypertensive encephalopathy

9. Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness
10. Prior maximum cumulative dose of doxorubicin >360 mg/m^2 or maximum cumulative dose of epirubicin >720 mg/m^2 or equivalent
11. Known hypersensitivity to trastuzumab, murine proteins, or excipients, or a general hypersensitivity to adhesives (**Cohort B** only)
12. History of severe allergic or immunological reactions, for example, difficult to control asthma.

General Exclusion Criteria:

13. Pregnancy or lactation
14. Unable or unwilling to comply with the requirements of the protocol, as assessed by the investigator
15. Concurrent enrollment in another clinical trial using an investigational anti-cancer treatment, including hormonal therapy, bisphosphonate therapy, and immunotherapy, within 28 days prior to the first dose of study treatment
16. Major surgical procedure or significant traumatic injury within 14 days prior to the first dose of study treatment or anticipated need for major surgery during the course of study treatment except for breast cancer surgery for patient receiving study drug in the neoadjuvant setting. Patients must be free of any clinically significant sequelae of prior surgery before they can receive their first dose of study treatment.
17. More than 12 weeks between the end of the last chemotherapy cycle and the first dose of study treatment, in case these treatments are initiated sequentially. This criterion does not apply to patients who are starting trastuzumab SC without previous or concurrent chemotherapy or concurrently with chemotherapy.
18. Current peripheral neuropathy of Grade 3 or greater per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0

No exceptions or waivers will be granted for the above listed inclusion and exclusion criteria.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

It is anticipated that approximately 2500 patients will be recruited into the study. Eligible patients with HER2-positive EBC will be allocated to one of the two following cohorts at the investigator's discretion:

- **Cohort A** (approximately 1800 patients): trastuzumab SC 600 mg via assisted administration into the thigh over a period of approximately 5 minutes using handheld syringes with hypodermic needles
- **Cohort B** (approximately 700 patients): trastuzumab SC 600 mg, first assisted, then self-administered into the thigh over a period of approximately 5 minutes using the SID. For enrollment into **Cohort B**, patients need to be willing to self-administer the study drug from the SID based on personal instructions/training provided by an HCP during the first assisted administration in addition to a quick reference guide and an instructional animation describing the injection device handling and use, including how to respond if the SID loses sufficient contact with the body.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

The investigational medicinal product (IMP) for this study is trastuzumab SC 600 mg supplied as vial and SID formulations:

- **Cohort A:** RO 045.2317/F07, manual SC injection formulation: trastuzumab SC 600 mg/5 mL vial
- **Cohort B:** RO 045-2317/F06, device formulation: trastuzumab SC 600 mg/5 mL prefilled, single-use injection device

According to the Medical Device Directive, the drug/device combination is considered an integral medicinal product and, therefore, as a single IMP for this study.

The drug product in the vials for manual injection (**Cohort A**) and in the SID (**Cohort B**) contains 120 mg/mL trastuzumab and 2000 U/mL rHuPH20 (manufactured in a Chinese hamster ovary cell line) acting as a permeation enhancer, histidine/histidine-HCl (buffer), alpha,alpha-trehalose dihydrate (bulking agent), methionine (stabilizer), and polysorbate 20 (stabilizer/emulsifier) in water for injection (WFI) at a pH of 5.5 ± 0.3.

The recommended storage conditions are 2–8°C protected from light for both trastuzumab SC formulations. Batch-specific details and information on shelf-life are given in the packaging label.

Trastuzumab for SC administration will be supplied by Roche. Packaging of trastuzumab for SC use will be overseen by the Roche Clinical Trial Supplies department. Each IMP unit will bear a label with the identification required by local law, the protocol number, drug identification, and dosage. The packaging and labelling of trastuzumab SC will be in accordance with Roche standard and local regulations.

For further details, refer to the Herceptin (RO 45-2317, Trastuzumab) IB.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Preparation and Administration of Trastuzumab for SC Injection

Cohort A: Trastuzumab SC for manual injection will be supplied in a vial containing a ready-to-use solution with a nominal content of 600 mg of trastuzumab. The solution is injected using a conventional handheld syringe fitted with a hypodermic needle. Further information on the preparation and administration is provided as a separate instruction leaflet.

Cohort B: Trastuzumab SC is supplied in a SID. The cartridge included in the device contains a nominal content 600 mg of trastuzumab. Information on the preparation and use of the SID is provided in the quick reference guide supplied with the SID.

The drug product must not be diluted and should be used according to the instructional leaflet provided separately. The solution should not be administered at 2–8°C. Details for equilibration of the device to room temperature can be found in the quick reference guide supplied with the SID.

The total time that trastuzumab SC (for manual injection and in a SID) is stable outside the fridge is 6 hours. Trastuzumab should be allowed to equilibrate prior to injection. The drug may be returned to the fridge if necessary, but it must be allowed to reach room temperature prior to administration, and the total time out of the fridge prior to administration must not exceed 6 hours.

Patients will be enrolled into one of two cohorts at the investigator's discretion.

All study treatment administrations will occur in a hospital setting as follows:

- **Cohort A**: Trastuzumab SC 600 mg will be injected subcutaneously by an HCP into the thigh over a period of approximately 5 minutes using a handheld syringe with a gauge 25 or 27 hypodermic needle.
- **Cohort B**: Trastuzumab SC 600 mg will be injected subcutaneously into the thigh over a period of approximately 5 minutes using the SID. The first administration will be assisted (performed by a HCP [physician or nurse]), and then following administrations may be self-administered into the thigh (if the patient is willing and judged competent by the HCP) over a period of approximately 5 minutes using the SID. During HCP-assisted administration, the HCP will assist the patient to use the SID to self-administer the dose. The HCP should moderate the level of assistance provided with an assessment of the patient's competence. Competent subjects will be asked if they are willing to continue by self-administration of the study drug from the SID. Willing patients will be allowed to self-administer the remaining trastuzumab SC doses under the direct supervision of a HCP. Patients assessed as not competent or are not willing to self-administer the study drug from the SID will have all the remaining trastuzumab SC doses administered by the HCP.

Those patients judged competent by the investigator and willing to self-administer remaining doses with the SID will be provided with training from the HCP during the first assisted administration and will be provided with instructional materials (a quick reference guide and an instructional animation describing the injection device handling and use, including how to respond if the SID loses sufficient contact with the body).

Patients will remain onsite to be observed for a period of 6 hours after start of their first trastuzumab administration and for 2 hours after the start of each subsequent trastuzumab administrations. Patients may be required to remain onsite for an extended period of time if considered clinically necessary by the investigator (e.g., emergence of AEs).

In addition to the study assessments described in Appendix 1, all clinical AEs that occur during the observation period, onset and resolution dates and times of AEs, the collection of detailed information about premedications prior to trastuzumab administration, and in addition to the date, the onset and resolution time of treatment of AEs occurring during the observation time will be collected.

The SID satisfaction questionnaire will only be completed by patients who have successfully completed a minimum of 2 self-administrations of the study drug in **Cohort B**.

For SID usability monitoring purposes, the first 48 patients enrolled in **Cohort B** will have their SID use monitored and recorded on the SID monitoring questionnaire by the trained HCP or investigator, intended to collect information about aspects of use related to usability of the device (see Appendix 7).

In the event of a SID failure which results in incomplete administration (injection of a portion of the full dose) to the patient, the missed portion of the trastuzumab SC dose may be manually administered from a vial. An instruction leaflet will be provided that will explain how to assess the amount needed to inject from a vial in the event of a SID failure. Subsequent doses should be administered using the SID. Device failures must also be reported to the Sponsor as a Medical Device Complaint (see Section 5.4.4). The device must then be returned via courier to Roche for assessment. In case of multiple (>1) device failures at different treatment cycles, the patient will revert to manual SC administrations of trastuzumab (using a conventional hand-held SC syringe) for all remaining cycles in order to complete 18 cycles in total as part of the study.

Any injection-related symptoms must have resolved before the patient is discharged, unless deemed clinically insignificant by the investigator. Patients who experience injection-related symptoms may be premedicated with paracetamol and antihistamines for subsequent injections.

4.3.2.2 Dose and Schedule of Trastuzumab SC

Trastuzumab SC treatment may be initiated after completion of neoadjuvant or adjuvant chemotherapy (sequentially), in combination with neoadjuvant or adjuvant paclitaxel or docetaxel chemotherapy (concurrently), or without adjuvant chemotherapy. In case of sequential treatment, the interval between the last dose of chemotherapy and the first dose of trastuzumab SC should not be longer than 12 weeks. For patients receiving trastuzumab SC with adjuvant chemotherapy, trastuzumab SC must be administered first, followed by the administration of chemotherapy. For patients receiving trastuzumab SC without neoadjuvant or adjuvant chemotherapy, the start of trastuzumab SC should be within a maximum of 3 months following surgery.

Patients in both cohorts will receive a fixed dose of 600 mg trastuzumab SC throughout the study, administered 3-weekly for a total of 18 cycles, unless disease recurrence, unacceptable toxicity, or patient withdrawal necessitates earlier treatment cessation.

Hormonal therapy and radiotherapy (if applicable) may be given concomitantly with trastuzumab SC, as per local guidelines.

Recommended chemotherapy regimens with trastuzumab to be followed in the adjuvant setting are as stated in the pivotal trials (see Table 1: sequential trastuzumab; HERA and NCCTG N9831: and concurrent trastuzumab; NSABP B31, B31 + N9831 and BCIRG 006). In the neoadjuvant-adjuvant setting, clinical Study MO16432 (NOAH), trastuzumab was administered concurrently with chemotherapy.

For neoadjuvant treatment, the following will be applied:

- In patients with early breast cancer eligible for neoadjuvant treatment, trastuzumab SC should only be used concurrently with low-dose anthracycline regimens (maximum cumulative doses: doxorubicin 180 mg/m^2 or epirubicin 360 mg/m^2).
- If patients have been treated concurrently with low-dose anthracyclines and trastuzumab in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery.
- After the neoadjuvant phase (8 cycles) of trastuzumab SC, patients will undergo surgery without interruption of trastuzumab treatment. After surgery, patients will receive additional 10 cycles of SC trastuzumab to complete 1 year of treatment with trastuzumab.
- Surgery should be planned after dosing at Cycle 8 without interruption of trastuzumab treatment.

4.3.2.3 Dose Modifications, Interruptions, and Delays

Administration of trastuzumab SC may be delayed to assess or treat adverse events, as detailed in Table 8.

Table 8 Management of Trastuzumab-Related Toxicity

Toxicity Related to Study Treatment	Action
Hematological and non-hematological, Grade 1 or 2 (excluding cardiac) toxicity	Continue with study treatment (all medication in the cycle)
Hematological and non-hematological, Grade 3 or 4 (excluding cardiac) toxicity	Hold study treatment (all medication in the cycle) until recovery to Grade ≤ 2. Toxicity resolved to Grade ≤ 2 within a maximum of 5 weeks calculated from last administration: Resume study treatment. Toxicity did NOT resolve to Grade ≤ 2 within a maximum of 5 weeks calculated from last administration: Discontinue trastuzumab permanently. Take patient off study drug. Continue treatment as deemed suitable by local investigator.
Recurrence of non-hematological, Grade 3 or 4 (excluding cardiac) toxicity upon re-challenge	Discontinue trastuzumab permanently. Take patient off study drug. Continue treatment as deemed suitable by local investigator.
Cardiac toxicity (significant asymptomatic drop in LVEF (≥ 10 percentage points from baseline and to a LVEF $< 50\%$)	Study treatment (all medication in the cycle) to be held, continued or resumed according to the algorithm depicted in Appendix 5.
Cardiac toxicity (symptomatic congestive heart failure)	Trastuzumab to be discontinued permanently (patient to be taken off study)
Cardiac toxicity (other than significant asymptomatic LVEF drop or CHF)	Actions must follow rules 1 to 3. For non-hematological toxicities
Hematological toxicity: Neutropenia $< 1.5 \times 10^9$/L	Hold study treatment (all medication in the cycle) until neutrophils $\geq 1.5 \times 10^9$/L.

For toxicity related to concurrently administered chemotherapy, specific instructions/actions should be followed in the relevant SmPC. In the case of chemotherapy-related hematological or non-hematological toxicity, the following action should be applied:

- Grade 1 or 2, continue trastuzumab treatment
- Grade 3 or 4, hold trastuzumab treatment until recovery to $\leq$ Grade 2

If the patient misses a dose of trastuzumab SC, then the usual dose should be given as soon as possible, with subsequent doses given every 3 weeks. No dose adjustment is needed in case of delayed administration of trastuzumab SC, as a fixed (600 mg) dose of trastuzumab is given for all SC cycles in this study.

Dose reductions are not permitted for toxicity. Patients who experience injection-related symptoms may be premedicated with paracetamol and antihistamines for subsequent infusions/injections.

4.3.3 Name of Additional Required Medication

Not applicable.

4.3.4 Investigational Medicinal Product Accountability

The investigator is responsible for the control of the drugs under investigation. Adequate records for the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the IMP must be maintained. Accountability and patient compliance will be assessed by maintaining adequate drug dispensing and return records.

Accurate records must be kept for each IMP provided by the Sponsor. These records must contain the following information:

- Documentation of IMP shipments received from the Sponsor (date received, quantity, and batch number)
- Disposition of unused IMP not dispensed to a patient
- A Drug Dispensing Log must be kept current and should contain the following information:

  Identification of the patient to whom the IMP was dispensed

  The date(s), quantity, and batch number of the IMP dispensed to the patient

4.3.4.1 Assessment of Compliance

The investigator is responsible for ensuring that the study drug is administered in compliance with the protocol. Delegation of this task must be approved by the investigator and clearly documented. Patient compliance will be assessed by maintaining adequate study drug dispensing records. All records and drug supplies must be available for inspection by the Roche Study Monitor at every monitoring visit.

Copies of the dispensing & inventory logs will be retrieved by the Monitor at study end.

4.3.4.2 Destruction of the IMPs

Used and unused IMP will be kept at the site (or designated pharmacy, depending on local practice) for accountability and destruction. Local or institutional regulations may require immediate destruction of used IMPs for safety reasons (e.g., cytotoxicity). In these cases, it may be acceptable for the investigational site staff to destroy the dispensed IMP before inspection by the Monitor, provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, and destroyed. Written authorization must be obtained from the Sponsor at study start up before destruction of unused trastuzumab SC can take place at a site.

Written documentation of destruction must contain the following:

- Identity (batch numbers and patient numbers) of the IMP(s) destroyed
- Quantity of the IMP(s) destroyed

- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the Sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs); it is recommended to burn the vials and SIDs at 1200°C.
- Name and signature of responsible person who discarded the IMP in a hazardous container for destruction

4.3.5 Post-Trial Access to Trastuzumab

Trastuzumab SC will only be provided to study patients for the protocol-defined 18 cycles. Subsequent treatment will be at the investigator's discretion and according to local practice.

4.4 CONCOMITANT THERAPY

All concomitant medications and prior treatments for breast cancer must be reported in the eCRF starting at the Screening visit. These include:

- Date and extent of primary surgery
- Any loco-regional radiation therapy (extent or volume and total dose)
- Any hormonal therapy and/or surgical and radiation-induced ovarian ablation and drug-induced ovarian suppression (type, drug name, dose and schedule, anticipated duration of therapy)
- Bisphosphonate therapy

Any additional medication that is necessary for the management of the patient may be used at the discretion of the investigator.

All concomitant medications are to be reported until the Safety Follow-up visit. Thereafter, only *the following medications* must be reported:

- Breast cancer treatments (e.g., hormonal therapy)
- Anti-cancer treatments given to treat a recurrence
- Medications related to the treatment of serious AEs

4.4.1 Permitted Therapy

In this study, trastuzumab SC treatment may be initiated after completion of neoadjuvant or adjuvant chemotherapy (sequentially), in combination with neoadjuvant or adjuvant paclitaxel or docetaxel chemotherapy (concurrently), or without adjuvant chemotherapy, or in combination with neoadjuvant chemotherapy followed by trastuzumab therapy for locally advanced (including inflammatory disease or tumors >2 cm in diameter). The choice of adjuvant chemotherapy will be at the investigator's discretion and according to standard of care for EBC.

Any medication which is necessary for the management of side effects of trastuzumab may be used at the discretion of the investigator. Paracetamol (acetaminophen), antihistamines, and other supportive medication may be used according to local clinical practice for the treatment of reactions associated with trastuzumab SC administration, including pyrexia.

Adjuvant tamoxifen (with or without a gonadotropin-releasing hormone agonist) or an aromatase inhibitor may be administered to patients with hormone receptor (estrogen and/or progesterone receptor) positive disease according to local practice. Adjuvant hormonal therapy and adjuvant radiotherapy (if indicated) may be given concomitantly with trastuzumab SC.

Patients may have started bisphosphonate therapy for a licensed indication before entering the study, and if so, this may continue. Bisphosphonate therapy (oral and IV only) can also be initiated during the study for the treatment of documented osteoporosis. If started during the trial, the patient must be assessed for evidence of progression first. The use of bisphosphonates for prevention of bone metastases is not allowed unless they become licensed for this indication during the study.

Other permitted concomitant therapies include:

- Supportive care, including transfusions, which should be prescribed according to local guidelines and the Investigator's clinical judgment
- Anti-emetic regimens may be used at the discretion of the investigator.
- Growth factors (i.e., G- or GM-CSF) may be used as clinically indicated according to institutional guidelines.
- Maintenance therapy for patients with chronic conditions, such as hypothyroidism, hypertension, diabetes, etc.
- Radiotherapy

Subcutaneous injections (e.g., insulin or heparin) are allowed as long as they are administered at a different injection site from that of the study drug (i.e., other than the thigh).

4.4.2 Prohibited Therapy

The following treatments are not permitted during trastuzumab SC treatment:

- Concurrent treatment with other systemic HER2-directed immunotherapy
- Concurrent investigational agents of any type
- Concurrent treatment of anthracyclines with trastuzumab in the adjuvant setting

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

4.5.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, and nutritional supplements) used by the patient starting from the Screening visit.

Demographic data will include age, gender, and self-reported ethnic origin.

4.5.1.2 Vital Signs

Vital signs include blood pressure, heart rate, and temperature measurements at screening and at the Safety Follow-up visit, as well as pre- and immediately post-trastuzumab SC administration at Cycles 1, 5, 9, 13, and 18. Vital signs measurements will be taken while the patient is in a seated position.

4.5.1.3 Physical Examinations

A general physical exam (including a general neurological exam, as clinically indicated) will be performed at screening, approximately 3-monthly during trastuzumab SC treatment (at Week 13/Cycle 5, Week 25/Cycle 9, Week 37/Cycle 13, and Week 52/Cycle 18), at the post-treatment Safety Follow-up visit, and subsequently according to the ASCO 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006) *or investigator's routine practice.* Physical examinations will be performed according to local practice; however, particular attention should be given to the cardiovascular system.

Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

4.5.1.4 Electrocardiograms

A standard 12-lead ECG needs to be performed as specified in Section 5.1.2 and in Appendix 1, Schedule of Assessments.

4.5.1.5 Performance status

Performance Status (PS) will be evaluated using the Eastern Cooperative Oncology Group (ECOG) PS Scale (see Appendix 2). The assessment will be performed at screening, approximately 3-monthly (every 4 cycles) during study treatment, and at the post-treatment Safety Follow-up visit, as specified in Appendix 1, Schedule of Assessments.

4.5.1.6 Other Clinical Safety Assessments

Refer to Section 5.1.2 for a description of cardiac safety assessments and Section 5.2.1 for instructions on documenting and handling adverse events.

4.5.1.7 Laboratory Assessments

4.5.1.7.1 HER2 Testing for Eligibility

To be eligible for the study, patients must have confirmed HER2 overexpression (by IHC) or HER2 gene amplification (by validated and approved methods at the local laboratories) in the invasive part of the tumor, defined as one of the following:

- A score of 3+ by IHC
- A positive ISH result

HER2 should be assessed in specialized local laboratories with an accurate and validated assay according to recommendations outlined in the SmPC for trastuzumab IV (Herceptin). HER2 status needs to be assessed prior to the first dose of study drug, but otherwise, there is no time limit for when this is to be performed.

4.5.1.7.2 Safety Laboratory Assessments

All hematology and blood chemistry laboratory tests will be completed at local laboratories. Normal ranges for a study site's local study laboratory parameters must be supplied to the Sponsor before the study starts.

Blood samples for hematology and biochemistry are scheduled at screening, on Day 1 of Cycles 9 (Week 25) and 18 (Week 52) of study treatment, and at the Safety Follow-up visit. Screening safety laboratory tests should be completed within 28 days prior to the first study treatment and should allow for an evaluation of all laboratory exclusion criteria as outlined in Section 4.1.2. Screening values should be used to confirm eligibility.

- Hematology tests include: hemoglobin, WBC and differential, ANC, and platelet count.
- Biochemistry tests include: creatinine, urea/blood urea nitrogen (BUN), serum ALT/glutamic pyruvic transaminase (SGPT), AST/serum glutamic oxaloacetic transaminase (SGOT), total bilirubin, ALP, albumin, sodium, potassium, and calcium.

For the purposes of this study, no additional samples are scheduled. However, additional assessments may be performed as per institutional practice, as clinically indicated. Results for samples other than those specified above (and listed in Appendix 1, Schedule of Assessments) will only be collected if associated with an AE.

4.5.1.7.3 Pregnancy Testing and Contraception

Females of childbearing potential (defined as premenopausal and not surgically sterilized or less than 1 year after the onset of menopause) will undergo a serum pregnancy test within 7 days prior to the first dose of trastuzumab SC. A positive pregnancy test at screening will lead to the exclusion of the patient. Subsequent pregnancy testing should be completed as clinically indicated for the duration of study treatment and until at least 7 months after the last dose of trastuzumab SC.

Women of childbearing potential and male participants with partners of childbearing potential must agree to use contraception during study treatment and for at least 7 months post-study treatment. Acceptable methods of contraception include:

- Complete abstinence* (if consistent with the preferred and usual lifestyle of the patient). Note: periodic abstinence (e.g., calendar, ovulation, symptothermal post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Male sterilization* (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients, the vasectomized male partner should be the sole partner.
- Non-hormonal intrauterine device or intrauterine system
- Barrier method:
    - Condom with spermicidal foam/gel/film/cream/suppository
    - Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

    *Considered highly-effective forms of contraception resulting in a low failure rate (i.e., less than 1% per year)

The following birth control methods are not considered acceptable in this study:

- Hormonal contraceptives (for females participating in the study)
- Periodic abstinence (e.g., calendar, ovulation, symptothermal post-ovulation methods) and withdrawal
- Single barrier methods (e.g., spermicides alone)

4.5.1.7.4 Immunogenicity and PK assessments (Subset of Cohort B)

Immunogenicity of trastuzumab SC and recombinant human hyaluronidase (rHuPH20) will be tested in a subset of patients enrolled in **Cohort B** at select sites. Sites interested in participating in the immunogenicity assessments will be selected and approved by Roche. Serum samples (for anti-trastuzumab antibody analyses) and plasma samples (for anti-rHuPH20 antibody analysis) will be drawn at baseline (after eligibility is confirmed, i.e., just before the first study treatment), on-treatment (pre-Cycle 9 dose, Week 25), and at least 6 months after the end of treatment. Since the evaluation of anti-trastuzumab assay results requires corresponding serum trastuzumab concentrations, the anti-trastuzumab analyses will be coupled with PK assessments.

The total blood loss for immunogenicity testing during the study is 18 mL. At each of the three assessment timepoints, approximately 6 mL of blood will be required for the rHuPH20 antibody analysis and trastuzumab antibody analysis, including confirmation of the presence of trastuzumab and the titer in serum.

The date/time of immunogenicity and PK sampling must be carefully recorded in all cases. On non-dosing days, the timing of sampling during the day will be at the investigator's discretion. Fasting is not a requirement for sampling.

In the event of an injection-related reaction, the blood samples for immunogenicity testing must be drawn within 8 hours following the reaction (see Appendix 1, Schedule of Assessments).

The serum and plasma samples (for anti-trastuzumab antibody and anti-rHuPH20 antibody analyses, respectively) will be stored on dry ice until shipment in batches can be arranged to the designated central laboratory. Details of sampling, handling, storage, and shipping are described in the study's Sample Handling and Logistics Manual.

A three-tiered analytical testing approach will be performed for HAHAs against both trastuzumab and rHuPH20. Screening for the potential emergence of antibodies will use bridging immunoassays. Any samples testing positive will be subsequently re-tested in a confirmatory assay. Finally, confirmed positives will be tested for the presence of neutralizing antibodies.

Samples will be kept for re-testing (if required) at the central laboratory and will be destroyed no later than 12 months after the Clinical Study Report (CSR) is finalized.

4.5.1.8 Breast Cancer Evaluations and Follow-Up

Patients will be assessed for residual disease (as per institutional practice) not more than 4 weeks before the first dose of study drug. Screening radiologic examinations to exclude metastatic disease should include a bilateral mammogram or breast MRI, and chest X-ray (CXR) or breast ultrasound. Should a previously taken chest CT or PET scan be available, then these results can also be used for eligibility assessment. These imaging tests do not need to be repeated if completed within 12 months prior to the first study treatment. In addition, bone scan and liver imaging should be performed if clinically indicated. During study treatment and the post-treatment follow-up period, patients will be followed for disease recurrence according to the American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up (Khatcheressian et al. 2006) *or investigator's routine practice* (see Appendix 1, Schedule of Assessments). In brief, the ASCO 2006 guidelines recommend:

- History/physical examination: every 3–6 months for the first 3 years after primary therapy, every 6 to 12 months for years 4 and 5, then annually
- Mammography: first post-treatment mammogram 1 year after the initial mammogram that led to diagnosis, but no earlier than 6 months after definitive radiation therapy. Subsequent mammograms should be obtained as indicated for surveillance of abnormalities.
- Pelvic examination: regular gynecologic follow-up is recommended for all women. Patients who receive tamoxifen should be advised to report any vaginal bleeding to their physicians.

- Routine blood tests: full blood counts and liver function tests are not recommended.
- Imaging studies: chest x-ray, bone scans, liver ultrasound, computerized tomography (CT) scans, fluorodeoxyglucose-positron emission tomography (FDG-PET) scans, and breast magnetic resonance imaging (MRI) are not recommended.
- Tumor markers: CA 15-3, CA 27.29, and CEA are not recommended.
- Accordingly, assessments for recurrence/relapse will be primarily by physical examination and questioning the patient, with additional tests as clinically indicated and according to routine practice.

4.5.1.8.1 Assessment of Recurrence

Disease-free survival (DFS) is a secondary endpoint in this study. DFS is defined as time from the date of first treatment to the date of local, regional, or distant recurrence; contralateral breast cancer; or death due to any cause.

The diagnosis of a first breast cancer recurrence or second primary cancer can be made only when clinical, radiological, and laboratory criteria are met. Acceptable methods of confirmation of recurrence include radiology, CT scan, brain scan, ultrasound, or cytology, as per local practice. In case of uncertainty, disease relapse should be confirmed by histological or cytological examination of a suspicious lesion, if possible. Some patients may develop a suspicious recurrence that leads to death quite quickly without having the possibility to confirm relapse of disease. Efforts should be made to obtain an autopsy report in such patients.

The earliest date of diagnosis of recurrent disease should be used and recorded. This should be based on clinical, radiological, histological, or cytological evidence. The recurrence of disease has to be backdated to the date of the first diagnosis of lesion (i.e., an objective finding), not to the date of occurrence of the first symptom.

Recurrent disease includes: local, regional, distant recurrence and contralateral breast cancer.

a) **Local recurrence**: In the ipsilateral breast after surgery:

In case of conservative surgery (lumpectomy): defined as evidence of tumor, except lobular carcinoma in situ, in the ipsilateral breast after mass excision.

In case of mastectomy, local recurrence (other than ipsilateral breast after lumpectomy): defined as evidence of tumor in any soft tissue or skin of the ipsilateral chest wall after mastectomy.

b) **Regional recurrence:** Defined as the development of tumor in the ipsilateral internal mammary and/or ipsilateral axillary lymph nodes, or extranodal soft tissue of the ipsilateral axilla. Regional recurrence does not include supraclavicular lymph nodes or tumor in the opposite breast.

c) **Contralateral invasive breast cancer:** Defined as development of invasive lobular or invasive ductal cancer in the contralateral breast (Hudis et al. 2007).

d) **Distant recurrence:** Defined as evidence of tumor in any area other than those described in subsections a) to c) above and the following:

- Skin, subcutaneous tissue, and lymph nodes (other than local or regional)
- Bone
- Bone marrow
- Lung
- Liver
- Central nervous system

4.5.1.9 Treatment Satisfaction with the SID

Patients in **Cohort B**, who went on to self-administration of the study drug will be asked to rate their overall satisfaction with trastuzumab SC administrations using the SID by completing a five-item SID satisfaction questionnaire. The questionnaire will be completed after the 4th cycle and at the Safety Follow-up visit (or at least 1 day after the last trastuzumab SC injection), after a minimum of 2 successful self-administrations of the study drug.

The questionnaire includes five items (level of comfort with the self-administration after training by a physician/nurse, convenience and ease of use, confidence with the administrations, overall satisfaction, and feedback on whether the SID would be chosen in the future), which will be rated on a 5-point Likert scale (from 1 = strongly disagree to 5 = strongly agree; see Appendix 6).

Completion of the questionnaire should take about 5 minutes.

For patients in **Cohort B** who discontinue study treatment prematurely for any reason, all efforts should be made to complete this questionnaire as part of the final assessment.

4.5.1.10 Pharmacoeconomic Assessments and Medical Care Utilization

In some countries and sites, MCU (e.g., time and motion) and/or pharmacoeconomic substudies will be conducted. Details of the substudies will be described in separate protocols.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

After consenting, patients will undergo the following screening procedures and assessments within 28 days prior to the first study treatment (denoted as Day 1), unless

otherwise specified or unless the procedure/assessment has already been conducted during this time period as part of the patient's routine clinical care:

- Demographics, complete medical history, and concomitant medications
- HER2 determination (Note: HER2 status needs to be assessed prior to the first dose of study drug, but otherwise there is no time limit for when this is to be performed.)
- General physical examination (including neurological examination, if clinically indicated)
- Measurement of vital signs (blood pressure, heart rate, and temperature), weight, and height
- ECOG performance status
- Cardiac assessments
    - Standard 12-lead ECG
    - LVEF is to be assessed within 14 days prior to the first study treatment if patients received anthracycline or 28 days prior to first study treatment for patients who received anthracycline-free regimens. Assessment should be performed by echocardiography (ECHO), multigated acquisition (MUGA) scan, or MRI (Note: ECHO is the preferred method).
    - Cardiac signs and symptoms
- Clinical laboratory testing (hematology, serum biochemistry) with results available prior to enrollment into the study to confirm patient eligibility (to be done in the allowed screening period of 28 days).
- Women of childbearing potential (defined as premenopausal, less than 1 year after the onset of menopause, or not surgically sterilized) will undergo a serum pregnancy test (β-HCG) within 7 days prior to the first dose of study treatment.
- **Cohort B** (selected sites only): Blood sample for immunogenicity testing (includes trastuzumab PK assessment)
- Imaging scan to exclude residual/recurrent disease per Section 4.5.1.8 (Note: results of imaging scans performed prior to obtaining informed consent and within 12 months prior to Day 1 may be used, i.e., such tests do not need to be repeated for screening.)
- Assessment of any SAEs caused by a protocol-mandated procedure

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment (also referred to as registration). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or document reasons for screening failure, as applicable. Data of patients who fail screening will not be entered into the eCRF and the clinical trials database.

Eligible patients will be allocated to either **Cohort A** or **Cohort B** at the investigator's discretion. For enrollment into **Cohort B**, patients need to be willing to self-administer

the study drug based on the instructions for use supplied with the SID and personal instructions provided by an HCP during the first assisted administration.

Upon enrollment, patients will be assigned a unique study patient identification number. A Patient Enrollment List must be maintained by the investigator. Enrollment and the start of study medication (Day 1) occur on the same day.

Please see Appendix 1 for the schedule of screening and pretreatment assessments.

4.5.2.2 Assessments during Treatment

All assessments must be performed on the day of the specified visit, unless a time window is specified in the schedule of assessments (see Appendix 1). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments.

The following assessments must be performed prior to the respective treatment visits, so that results are available prior to dosing: hematology and biochemistry, LVEF, and routine breast cancer follow-up assessments.

Patients will undergo the following assessments during the study treatment period:

Assessments performed at each treatment visit:

- Assessment of AEs (including SAEs)
- Observation time for patients in **Cohort B**
- SID monitoring for subgroup of patients in **Cohort B**
- Treatment compliance
- Concomitant medication
- Survival follow-up

Assessments performed at specified intervals:

- Routine breast cancer follow-up, performed according to the ASCO 2006 Guideline for Breast Cancer Follow-up (Khatcheressian et al. 2006) *or investigator's routine practice* and reported every 6 months or per institutional standard practices (see Section 4.5.1.8)
- General physical examination (including neurological examination, if clinically indicated) will be performed on a 3-monthly basis (every 4 cycles).
- Weight will be measured for all patients at screening. For **Cohort B** patients participating to immunogenicity and PK testing at Cycle 9 (Week 25).
- Vital signs measurement (blood pressure, heart rate, and temperature) pre- and immediately post-trastuzumab SC administration on a 3-monthly basis (every 4 cycles; i.e., at Cycles 1, 5, 9, 13, and 18).

- Cardiac assessment (ECG, LVEF, and cardiac signs and symptoms) and evaluation of ECOG performance status performed on a 3-monthly basis (every 4 cycles);
- Hematology and biochemistry at Cycles 9 (Week 25) and 18 (Week 52);
- Blood samples for immunogenicity and PK testing (a subset of **Cohort B** patients at selected study sites) prior to Cycle 9 (Week 25)
- SID satisfaction questionnaire after the 4th treatment cycle (**Cohort B** patients who have successfully completed a minimum of 2 self-administrations of the study drug)
- Pregnancy test completed as clinically indicated

Please see Appendix 1 for the schedule of assessments performed during the treatment period.

4.5.2.3 Assessments at Treatment Completion/Early Termination: Safety Follow-Up Visit

Patients who complete the study treatment period (18 cycles of trastuzumab SC) or discontinue the study treatment early will be asked to return to the clinic 4 weeks after their last dose of trastuzumab SC for a Safety Follow-up visit. The following assessments will be completed at the Safety Follow-up:

- Physical exam (including neurological examination, if clinically indicated)
- Vital signs (blood pressure, heart rate, and temperature), ECOG performance status
- Assessment of AEs (including SAEs) and concomitant medication
- Cardiac safety assessments, if clinically indicated (see Section 5.1.1.2 for details)
- Clinical laboratory testing (hematology and serum biochemistry)
- SID satisfaction questionnaire (**Cohort B** patients only who have successfully completed a minimum of 2 self-administrations of the study drug) at least 1 day after the last trastuzumab SC injection

4.5.2.4 Post-treatment Follow-up Visits (minimum 5 years)

All patients will be followed-up for cancer recurrence and survival till study end (i.e., until all patients have had a minimum 5-year follow-up) yearly or at higher frequency based on the site standard of care. The duration of follow-up will be at least 5 years after the last study treatment or until withdrawal from the study, lost to follow-up, or death, whichever occurs first. During this post-treatment follow-up period, patients will undergo the following assessments:

- Breast cancer follow-up according to the ASCO 2006 Guideline for Breast Cancer Follow-up (Khatcheressian et al. 2006) and reporting every 6 months or as per institutional standard practices (see Section 4.5.1.8 for details)
- Blood samples for immunogenicity and PK analyses will be collected from a subset of **Cohort B** patients (at selected sites only) 6 months after their last study treatment.

- Patients' weight must also recorded 6 months after their last study treatment if participating to immunogenicity and PK testing.
- Pregnancy test as clinically indicated up to *7* months after last study treatment
- AE follow-up: *After initiation of study drug,* all AEs/SAEs (except unrelated non-cardiac AEs in the follow-up period), regardless of relationship to study drug, will be reported until study closure. The investigator does not need to actively monitor subjects for AEs once the trial has ended. However, if becoming aware of any serious adverse events and non-serious adverse events of special interest occurring to a subject, the investigator should report those to the sponsor (see Section 5.6).
- Concomitant medications: Only *breast cancer treatments (e.g., endocrine therapy), anti-cancer treatments given to treat a recurrence, and medications related to the treatment of SAEs will* be *recorded*; refer to Section 4.4 for details.
- Cardiac safety assessments will be performed at 6, 12, and 24 months and at yearly intervals until 5 years after treatment cessation (see Section 5.1.1.2 for details);
- Survival: After disease progression, patients will be managed as per local practice and followed for survival only.

After study treatment completion (or early discontinuation), AEs should be followed as outlined in Section 5.5 and Section 5.6.

Please see Appendix 1 for the schedule of follow-up assessments.

4.5.2.5 Assessments at Unplanned Visits

Assessments other than those specified in Appendix 1, Schedule of Assessments, may be performed as clinically indicated and need to be adequately documented.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Patients should be informed of circumstances under which their participation may be terminated by the investigator or the study Sponsor without the patient's consent and in case of such withdrawal, the reason(s) for withdrawal must be documented and explained to the patient.

Patients have the right to withdraw from the study at any time for any reason. Should a patient decide to withdraw, all efforts should be made to complete and report the observations prior to withdrawal as thoroughly as possible. Patients will not be followed for any reason after consent has been withdrawn.

4.6.1.1 Discontinuation from Study Drug

Reasons for study drug discontinuation may include, but are not limited to the following:

- Withdrawal of consent by the patient
- Pregnancy
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if she or he continues receiving the study drug
- Investigator or Sponsor determines it is in the best interest of the patient
- Intercurrent illness
- AE(s)
- Treatment failure
- Protocol violation
- Lack of compliance with the study and/or study procedures (e.g., dosing instructions or study visits)
- Cure

Patients refusing further study treatment should be asked if they can still be contacted for further information after treatment cessation. The outcome of that discussion should be documented in both the medical records and in the eCRF.

Patients who discontinue study treatment prematurely due to lack of tolerability will be clinically managed as per local practice and followed as outlined in the Schedule of Assessments, Appendix 1. If the reason for treatment discontinuation is an AE, the principal specific event will be recorded in the eCRF.

All prematurely withdrawn patients who have received at least one dose of trastuzumab should continue to be monitored for cardiac function as described in the Herceptin SmPC, within or outside the study, as appropriate.

4.6.1.2 Withdrawal from Study

Reasons for withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent by the patient
- Treatment failure
- Protocol violation

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided, and all withdrawals should undergo a complete final evaluation at the time of termination, which should include documentation and an explanation of the reason for withdrawal.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the

appropriate eCRF. If lost to follow-up, the investigator should contact the patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal.

Enrolled patients who are prematurely discontinued from the study will not be replaced, irrespective of the reason for withdrawal.

4.6.2 Study and Site Discontinuation

The Sponsor and study Steering Committee have the right to terminate the study at any time. Should this be necessary, the required procedures will be implemented after review and consultation with the Steering Committee. In terminating the study, Roche and the investigators will assure that adequate consideration is given to the protection of the patient's interests. The appropriate IEC and Regulatory Agencies will be informed accordingly.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Noncompliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 General Safety Assessments

Patients will be assessed by prior medical history, vital signs (including blood pressure, heart rate, temperature), weight and height (screening only), physical examination, adverse events, and concomitant medications. A complete medical history (including demographic profile and prior treatments for cancer) will be documented at screening. A general physical exam (including general neurological exam, as clinically indicated) will be performed at screening, approximately 3-monthly (every 4 cycles) during trastuzumab SC treatment, at the post-treatment Safety Follow-up visit, and subsequently according to the ASCO 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006) *or investigator's routine practice* during the 5-year follow-up period (see Appendix 1, Schedule of Assessments). During physical examination, particular attention should be given to the cardiovascular system. Apart from physical exams, SC injection sites will be checked at every visit, and blood pressure will be measured before and after trastuzumab SC administration every 4 cycles, as specified in Appendix 1, Schedule of Assessments.

Adverse events will be monitored and documented continuously during study (at each 3-weekly treatment visit and during the post-treatment follow-up, as detailed in Section 5.3.1). Serious adverse events will also be monitored, documented, and reported; refer to Section 5.4.2 and Section 5.5 for details on SAE reporting and follow-up requirements, respectively. All AEs and SAEs (including patients' symptoms and signs of toxicity and clinically significant hematological and biochemical parameters) will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 5). Changes in concomitant medication will be recorded at each study visit.

5.1.1.1 Observation Time Assessment

In addition to the study assessments described in Appendix 1, all clinical AEs that occur during the observation period will be collected for all patients in **Cohort B** (within 6 hours after start of the first trastuzumab administration or within 2 hours after start of following trastuzumab administrations). Data collected during the observation period will include: Frequency, incidence, and grade of AEs; onset and resolution times of AEs (dd:mm:yyyy:hh:mm); outcome of AEs; and details of treatments provided following AEs during the observation period.

5.1.1.2 Cardiac Safety Assessments

Cardiac function will be evaluated regularly throughout the study by measuring LVEF using echocardiography, MUGA scan, or MRI (method selected according to local practice); ECG; and assessment of cardiac signs and symptoms.

Cardiac safety assessments will be performed at screening, approximately 3-monthly during trastuzumab SC treatment (at Week 13/Cycle 5, Week 25/Cycle 9, Week 37/Cycle 13, and Week 52/Cycle 18; with the results available prior to trastuzumab administration) and then at 6, 12, and 24 months, and 3, 4, and 5 years after treatment cessation (see Appendix 1, Schedule of Assessments). LVEF assessment should be performed at the Safety Follow-up visit (4 weeks after the end of treatment) only if clinically indicated.

5.1.1.3 LVEF Assessment

The screening LVEF assessment should be performed within 14 days for prior anthracycline use or within 28 days prior to the first trastuzumab SC administration for anthracycline-free regimens, and the LVEF must be $\geq$55% for the patient to be eligible for participation in this study. The method of assessment (echocardiography, MUGA, or MRI) is at the investigator's discretion; however, to the extent possible, the same imaging technique is to be used for each patient throughout the study. LVEF assessment results must be available before/on the day of the next scheduled trastuzumab administration, and, should a reduction in LVEF be noticed compared to screening, a decision to give or hold that dose must be made based on the algorithm provided in Appendix 4. In addition, any patient who develops clinical signs or symptoms suspicious of cardiac failure at any time during the study should undergo an

LVEF assessment immediately. If a patient has an LVEF result between 45%–49%, a drop of ≥10% and is symptomatic, or is a patient for whom the study drug was permanently stopped due to a significant drop in LVEF, then a repeat LVEF should be performed as clinically indicated, with a minimum repeat LVEF within 3 weeks.

Of note, if MUGA scans are chosen, investigators must be aware that there may be local guidelines which govern how many MUGA scans (or the amount of irradiation) a patient is allowed to have in a year and must ensure that patients are able to adhere to the cardiac assessment schedule as outlined in Appendix 1. In case additional LVEF assessments become necessary for the medical management of a patient, the investigator may use echocardiography instead of a MUGA scan to remain within the locally accepted amount of irradiation.

Symptomatic left ventricular dysfunction (congestive heart failure) will be graded according to NCI-CTCAE version 4.0 (Appendix 5) and the New York Heart Association (NYHA) functional classification (Appendix 3).

5.1.2 Management of Specific Adverse Events

Cardiac safety will be monitored throughout the study, as described in Section 5.1.1.2. In addition to the scheduled assessments, any patient who develops clinical signs or symptoms suspicious of cardiac failure at any time during the study should undergo an LVEF assessment immediately. Patients whose LVEF falls ≥10 percentage points from screening and to a LVEF <50% may require temporary or permanent cessation of trastuzumab in accordance with the treatment continuation/discontinuation algorithm shown in Appendix 4. A repeat LVEF assessment should be performed approximately 3 weeks later. If the LVEF has not improved or has declined further, trastuzumab should be discontinued. All such patients should be referred for assessment by a cardiologist and followed up. Trastuzumab should also be discontinued in any patient who develops clinically significant heart failure see (Section 4.3.3).

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.8 and Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.1.1 Laboratory Test Abnormalities

Local laboratories will be used for all safety laboratory tests. Laboratory test reports should be included in the patient chart and made available for routine monitoring and source document verification.

Any treatment-emergent abnormal laboratory result that is clinically significant should be recorded as a single diagnosis on the AE page in the eCRF. Clinical significance is defined as meeting one or more of the following conditions:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption, or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)

Laboratory test value abnormalities that are not considered clinically significant should not be recorded as AEs in the eCRF. Laboratory test results obtained at timepoints other than those specified in Appendix 1 will only be recorded on the laboratory results e-form of the eCRF, if they are associated with an AE.

Any laboratory result abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

5.2.2 Serious Adverse Events (Immediately Reportable to Roche)

A SAE is an experience that suggests a significant hazard, contraindication, side effect, or precaution. It is any AE that at any dose fulfils at least one of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The term sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably.

Please refer to Section 5.4 and Section 5.5 for details on how these events should be reported and followed up, respectively.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to NCI-CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF. Serious adverse event s are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 to Section 5.6.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

The investigator is also responsible for reporting medical device complaints, regardless whether they are associated with adverse events or not (see Section 5.4.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies). All other adverse events will be recorded as medical history.

After initiation of study drug, all AEs/SAEs *(except unrelated non-cardiac AEs in the follow-up period)*, regardless of relationship to study drug, will be reported until study closure. The investigator does not need to actively monitor subjects for AEs once the trial has ended. However, if becoming aware of any serious adverse events and non-serious adverse events of special interest occurring to a subject, the investigator should report those to the Sponsor (see Section 5.6).

Any injection-site reactions are considered to be related AEs/SAEs and should be reported accordingly.

Symptomatic congestive heart failure must be reported irrespective of causal relationship during the full course of the study, even if the patient starts a new anticancer regimen.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of nondirective questioning should be adopted for eliciting adverse event information at all patient evaluation time points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The intensity of all adverse events will be graded according to the NCI-CTCAE, version 4.0 on a five-point scale (Grade 1 to 5) and reported in detail on the eCRF.

Table 9 will be used for assessing severity for AEs that are not specifically listed in the NCI-CTCAE.

Table 9 Assessment of AE Severity

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
Grade 2	Moderate	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
Grade 3	Severe	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
Grade 4	Life threatening	Life-threatening consequences or urgent intervention indicated [d]
Grade 5	Death	Death related to adverse event [d]

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving trastuzumab SC concurrently with adjuvant chemotherapy, causality will be assessed individually for each therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct English medical terminology/concepts when recording AEs on the Adverse Event eCRF. Colloquialisms and abbreviations should be avoided.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

For all adverse events, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF.

For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by a mild, nonserious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

Recurrence of breast cancer (as defined in Section 4.5.1.8.1) should not be reported as an AE since this is clearly consistent with progression/relapse of the underlying disease. Hospitalization due solely to the relapse of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of relapse may be reported as AEs if the symptom cannot be determined as exclusively due to the relapse of the underlying malignancy or does not fit the expected pattern of relapse for the disease under study.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated

potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator’s judgment

It is the investigator’s responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor within 24 hours after learning of the event, as a serious AE (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur prior to study closure that are attributed by the investigator solely to progression of EBC should be recorded only on the *Death* eCRF *page*. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

During study survival follow-up, deaths attributed to progression of EBC should be recorded only on the *Death* eCRF *page*.

5.3.5.8 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of the Underlying Condition

Medical occurrences or symptoms of deterioration that are anticipated as part of the patient's underlying breast cancer should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of breast cancer on the Adverse Event eCRF, it is important to convey the concept that the

condition has changed by including applicable descriptors (e.g., “accelerated breast cancer”).

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. The determination of clinical progression will be based on objective evidence and/or symptomatic deterioration. Every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration)
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
    - The patient has not suffered an adverse event
- Hospitalization due solely to progression of the underlying cancer

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfils serious criteria, the event should be reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The investigator must report the following events to the Sponsor within 24 hours after becoming aware of the event, regardless of relationship to study drug:

- SAEs (see definition in Section 5.2.2)
- Pregnancies (for female study patients and female partners of male study patients)
- Device complaints

Investigators must also comply with local requirements for reporting SAEs to the local health authority and EC.

Serious adverse events regardless of the relationship to the study drug ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. All participating investigators and the respective independent Ethics Committees (ECs) will be notified of all Suspected Unexpected Serious Adverse Reactions (SUSARs) that are reported during the study. An AE only qualifies as a SUSAR when all of the following conditions are met:

- The event is serious (SAE);
- The event is deemed related to the study drug, according to the criteria provided in Section 5.3.4. (Note: any suspicion of a causal relationship should lead to an assessment of 'related');
- When assessed against the known safety profile of trastuzumab SC (as described in the IB), the event is considered unexpected (not foreseen in the IB).

When all patients at a particular site are off treatment as defined by the protocol:

- Individual SUSAR reports originating in that particular trial will be forwarded to all participating investigators and the IECs associated with their sites, on an expedited basis;
- Individual SUSARs considered to be a significant safety issue and/or which result in Roche recommending a change to the Informed Consent Form (ICF), will be reported in an expedited manner to all investigators and reviewing IECs;
- SUSAR reports originating from other trials using the same IMP will be provided as six-monthly SUSAR Reports (SSRs) to all investigators and IECs where long-term follow-up studies are carried out.

5.4.1 Emergency Medical Contacts

Medical Monitor (Roche Medical Responsible) Contact Information

Primary Contact

Medical Monitor: [redacted] M.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Secondary Contact

Medical Monitor: Dr. [redacted] M.D.

Telephone No.: *+650 225-1000*

Office Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Centre Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Centre Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events

For reports of serious adverse events, investigators should record all case details that can be gathered within 24 hours on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management or its designee by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event CRF and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the event, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

The investigator should report all complaints relating to the medical device used to administer the study treatment to Roche. The investigator must document as much information as possible (based on the *Medical Device Complaint Form*) including the batch number and expiration date of the device and forward this to Roche Safety Risk Management or its designee within 24 hours of becoming aware of the complaint. The investigator may also be requested to forward defective medical device samples to Roche.

If the medical device complaint results in an AE, the information should be captured on the patient eCRF. If the medical device complaint results in an SAE, the investigator should also complete an *SAE Reporting Form* and forward it to Roche Safety Risk Management within 24 hours of becoming aware of the event.

According to Roche standard procedures, all AE reports/complaints from the use of investigational medicinal products (IMPs) that are associated with a Medical Device which is used to administer the IMP must be forwarded to Drug Safety and all AE reports/complaints associated with a Medical Device, and all Medical Device SAEs must

be forwarded to the Local Complaint Manager/relevant department for complaint management. In addition, all medical device SAEs need to be reported within 24 hours to Roche Safety Risk Management or its designee.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

For women of childbearing potential (defined as premenopausal, less than 1 year after the onset of menopause or not surgically sterilized), appropriate contraceptive measures are mandatory during study treatment (see Section 4.5.1.7.3). Based on pharmacokinetic considerations, contraceptive measures are recommended for at least 7 months following the last dose of trastuzumab.

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 7 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue the study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the pregnancy, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). As soon as the EDC system is operating, the Pregnancy Report eCRF will be completed.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

The investigator must report all medical device complaints to Roche Safety Risk Management. The investigator should document as much information as possible on the Medical Device Complaint Form, including the product batch number and expiration date and forward this to Roche Safety Risk Management within 24 hours of knowledge of the complaint. The investigator may also be requested to forward defective medical device samples to Roche.

If the medical device complaint results in an AE, the Medical Device Complaint eCRF must be completed and submitted through the EDC within 24 hours after learning of the event. The AE must be reported on the Adverse Event eCRF. If the medical device complaint results in an SAE, the investigator should also complete an *SAE Reporting Form* and forward it to Roche Safety Risk Management within 24 hours of knowledge, as outlined in Section 5.4.2.

In the event of a device failure, the complaint must be reported to Roche Safety Risk Management. The device must also be returned via courier to Roche for assessment. Supplemental dosing requirements for the patient will be assessed by the investigator as per the instructions provided. In the case of a patient experiencing more than one device failure the patient will revert to SC trastuzumab for all remaining cycles to complete 18 cycles in total as part of the study.

The investigator should report all complaints relating to the medical device used to administer the study treatment to Roche Safety Risk Management. The investigator must document as much information as possible (based on the Medical Device Complaint Form [gcp_for000447]) including the batch number and expiration date and forward this to Roche Safety Risk Management within 24 hours of knowledge of the complaint. The investigator may also be requested to forward defective medical device samples to Roche.

If the medical device complaint results in an AE, the information should be captured on the patient eCRF. If the medical device complaint results in an SAE, the investigator should also complete an *SAE Reporting Form* [gcp_for004369] and forward it to Roche Safety Risk Management within 24 hours of knowledge.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

The Investigator must report new significant follow-up information for these events to the Sponsor within 24 hours after becoming aware of the information. New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event (including outcome of a reported pregnancy, as applicable)

In an individual patient, AE follow-up will continue as follows:

Related *or cardiac* AEs and SAEs will be followed until one of the following occurs:

- Resolved or improved to baseline state
- Relationship is reassessed as unrelated
- Investigator confirms that no further improvement can be expected
- Start of a new anti-cancer regimen
- Death

Unrelated *non-cardiac* AEs *(Grade 3 or Grade 4)* and SAEs *(any grade)* will be followed until one of the following occurs:

- Resolved or improved to baseline state
- Severity improved to Grade 2
- Investigator confirms that no further improvement can be expected
- Start of new anti-cancer regimen
- Death

Unrelated *non-cardiac* AEs (Grade 1 or Grade 2) will be followed until 4 weeks after the last dose of study drug in an individual patient.

The final outcome of each adverse event must be recorded on the eCRF.

Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range or baseline state and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

At the *final* follow-up visit *of the study*, the Investigator should instruct each patient to report to the Investigator any subsequent adverse events. The Sponsor should be notified if the Investigator becomes aware of any death or serious adverse event *related to study drug,* occurring at any time, after a patient has discontinued study participation, even after study closure. The investigator is not required to actively monitor patients after the study has ended.

The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The Investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the Investigator should report these events, indefinitely, directly to Roche Safety Risk Management via telephone (see "Protocol Administrative and Contact Information & List of Investigators").

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, AND ETHICS COMMITTEES

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Herceptin (RO 45-2317, Trastuzumab) IB

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 2500 patients is planned for this study (approximately 1800 patients in **Cohort A** and approximately 700 patients in **Cohort B**). There is no formal statistical hypothesis; hence, all safety (primary) endpoints results will be presented by 95% confidence intervals and descriptively explained.

For the purpose of the estimation of sample size, the incidence/proportion of congestive heart failure (CHF)-related SAEs was chosen as a safety endpoint of primary interest.

Table 10 below includes 95% Clopper-Pearson confidence intervals for CHF-related SAE incidence range between 1% and 10%.

Table 10 Clopper-Pearson 95% Confidence Intervals for the Observed CHF-Related SAE Incidence

Cohort A: **Total number of patients: 1800**	
Number of patients with CHF-related SAEs (incidence rate)	**95% Clopper Pearson CI**
18 (1%)	0.1%–1.6%
36 (2%)	1.4%–2.8%
72 (4%)	3.1%–5.0%
108 (6%)	5.0%–7.2%
144 (8%)	6.8%–9.4%
180 (10%)	8.7%–11.5%
Cohort B: **Total number of patients: 700**	
7 (1%)	0.04%–2.1%
14 (2%)	1.1%–3.3%
28 (4%)	2.7%–5.7%
42 (6%)	4.4%–8.0%
56 (8%)	6.1%–10.3%
70 (10%)	7.9%–12.5%

CI = Confidence Interval; CHF = congestive heart failure; SAE = serious adverse event.

Therefore, based on an observed CHF-related SAE incidence rate of 4% (Romand et al. 2005; Ewer and O'Shaughnessy 2007) and a sample size of 1800 patients in **Cohort A**, the upper limit of the 95% confidence interval (CI) for the incidence rate will be 5.0%. For **Cohort B**, the same CHF-related SAE incidence rate and a sample size of 700 patients will give an upper limit of the 95% CI of 5.7%.

The estimation of the sample size is produced by the SAS program and nQuery Version 6.

The split of the two cohorts in the current study was based on the availability of the device, which was planned to be due by the end of 2012. The planned patient size was then further supported by the sample size calculation for the target event of CHF-related SAEs. Based on an observed CHF-related SAE incidence rate of 4% (Romand et al. 2005; Ewer and O'Shaughnessy 2007) and a sample size of 700 patients for **Cohort B**, the upper limit of the 95% CI for the incidence rate will be 5.7%. CHF-related SAE events (N = 28) (4%) CI 2.7%–5.7%.

In **Cohort B** only, exploratory analyses on the usability of the SID summarizing the parameters collected via SID monitoring questionnaire (Appendix 7) will be provided to

the first 48 patients enrolled who were judged able and were willing to self-administer remaining doses from the SID under direct observation of the HCP. A sample size of 48 patients using the SID for 17 cycles to self-administer a dose without assistance equates to sample of n=816 dosing events. If 0 events occur in this sample of trials, it can be stated with 99% confident it will be <1% in the true population. The Adjusted Wald Approximate lower-limit of one-sided confidence interval for binomial distributed proportions statistical model has been used.

Refer to the Statistical Analysis Plan (SAP) for further details.

6.2 SUMMARIES OF CONDUCT OF STUDY

This is a Phase III prospective, two-cohort, non-randomized, multicenter, multinational, open-label study. Eligible patients with HER2-positive EBC will be allocated to one of two cohorts at the investigators' discretion:

- **Cohort A** (approximately 1800 patients) will receive trastuzumab SC by assisted administration using a conventional syringe.
- **Cohort B** (approximately 700 patients) will receive trastuzumab SC, first assisted, then self-administered (select patients) using a SID.

Patients in both cohorts will receive a total of 18 cycles of trastuzumab SC, unless disease recurrence, unacceptable toxicity, or patient withdrawal necessitates earlier treatment cessation. During adjuvant therapy, patients will be assessed for safety and efficacy, as detailed in Appendix 1.

Safety endpoints are the primary objectives in this study. Secondary efficacy endpoints include DFS, OS (both cohorts), and patient satisfaction with trastuzumab SC administration using the SID (**Cohort B** patients who went on to self-administration only). In addition, immunogenicity of trastuzumab and rHuPH20 (with PK) will be analyzed in a subset of patients enrolled in **Cohort B** at select sites. There is no formal statistical hypothesis for the comparison of **Cohort A** and **Cohort B**. With the exceptions noted above, all summaries and analyses will be performed for **Cohort A** and for **Cohort B**.

The primary analysis of safety endpoints and a preliminary analysis of efficacy (DFS, OS) will take place when all patients have received 18 cycles of trastuzumab SC and have completed the post-treatment Safety Follow-up assessments. The final analysis of OS and DFS and updated summaries for safety parameters will be performed when the last patient has been followed up for at least 5 years after her/his last study treatment, or earlier, if one of the following is documented for all treated patients: withdrawal of consent, loss to follow-up, or death. This is expected to take place approximately 8 years after the enrollment of the first patient, based on an expected 18-month recruitment period per cohort, 12 months of study treatment and 5 years of follow-up

after the last study treatment: There will be no adjustments for multiplicity of endpoints or within-subgroups comparisons.

Three interim safety analyses are planned for the study when approximately 500, 1000, and 2500 patients have received at least one trastuzumab SC injection. More details are provided in the Section 3.1.2 of the protocol and in the Steering Committee Charter.

A Clinical Study Report (CSR) will be written at the time of the primary endpoint analysis, and distributed to Health Authorities in keeping with the applicable regulatory requirements. All subsequent data analyses will be reflected in an addendum to the CSR.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Not applicable; no formal statistical comparisons of the two cohorts are planned.

6.4 SAFETY ANALYSES

6.4.1 Primary Safety Endpoint

Safety endpoints are the primary objectives in this study and will include: all AEs, Grade ≥3 AEs, SAEs, AEs leading to premature discontinuation of study treatment, AEs causing interruption of trastuzumab SC, cardiac AEs, CHF-related SAEs, premature withdrawals from study and study medication, exposure to treatment, laboratory parameters, LVEF, vital signs, ECG, weight, and ECOG performance status.

The primary analysis of the safety endpoints will be performed for the safety population (SP) defined as all enrolled patients who received at least one dose of study medication. There will be two safety populations, one for each cohort (SP1 for **Cohort A** and SP2 for **Cohort B**). The safety endpoints will be summarized for each cohort (SP1 and SP2) and overall (SP) as described below. The primary analysis of safety endpoints will take place when all patients have received 18 cycles of trastuzumab SC and have completed the post-treatment Safety Follow-up assessments. Updated summaries for safety parameters will be prepared when the last patient has been followed up for at least 5 years after her/his last study treatment, or earlier, if one of the following is documented for all treated patients: withdrawal of consent, loss to follow-up, or death.

The analysis of AEs will focus on treatment-emergent adverse events (TEAEs) i.e, AEs occurring on the day of or after first administration of study drug. Non-treatment emergent AEs (i.e., those occurring before commencement of study medication) will only be listed. The incidence of AEs, AEs leading to premature discontinuation or interruption of study treatment, SAEs, Grade 3 and 4, and cardiac AEs will be summarized according to the primary system-organ class (SOC) and within each SOC by MedDRA preferred term. The time to onset of the first episode of cardiac AEs will also be summarized using the Kaplan-Meier approach. The incidence of deaths and cause of deaths will be listed and summarized by treatment cohort and overall.

LVEF will be summarized over time by means of mean, median, and range (mean and maximum) and will be presented graphically for each trastuzumab SC cohort and overall. Vital signs, ECG, and weight will be summarized similar to LVEF.

Safety laboratory parameters (hematology, biochemistry, as defined in Section 4.5.1.7.2), will be presented in shift tables according to NCI CTC grade at screening versus worst grade during trastuzumab treatment for each trastuzumab SC cohort and overall. The summary of laboratory parameters will include means, standard deviation, minimum, and maximum values. Select laboratory parameters may also be displayed graphically. More details will be presented in the SAP.

Exposure to study treatment (number of cycles administered) and duration of treatment exposure (calculated from date of first study treatment to the last treatment date) will be summarized.

The number of patients who prematurely discontinue study treatment and the number of patients who withdrew from the study will be summarized, and reasons for withdrawal will be displayed.

ECOG performance status will be summarized by frequency tables over time, and percentage of patients in different categories will be presented by bar charts at different timepoints.

6.5 EFFICACY ANALYSES

6.5.1 Secondary Efficacy Variables

Secondary efficacy endpoints include disease-free survival (DFS) and overall survival (OS) and will be assessed in both cohorts.

- DFS is defined as the time from the date of first treatment to the date of local, regional, or distant recurrence; contralateral invasive breast cancer (including contralateral or ipsilateral ductal carcinoma in situ [DCIS]); or death due to any cause.
- OS is defined as time from the date of first treatment until date of death, regardless of the cause of death.

DFS and OS will be analyzed as a time-to-event variable for the ITT population (see Section 6.5.2).

In addition, patients' satisfaction with trastuzumab SC administration using the SID will be evaluated for **Cohort B** patients who went on to self-administration only.

6.5.2 Analyses of Efficacy Endpoints

The efficacy endpoints, DFS and OS, will be analyzed as a time-to-event variable for the ITT and PP populations and for each cohort. Estimates and corresponding 95% confidence intervals for the survivor function for the time-to-event variable will be

obtained by using the KM approach. A frequency table will be also provided for the type of DFS event (e.g., local, regional, or distant recurrence; contralateral *breast cancer*; or death).

A preliminary analysis of efficacy (DFS and OS) will take place when all patients have received 18 cycles of trastuzumab SC and have completed the post-treatment Safety Follow-up assessments. The final analysis of OS and DFS will take place when the last patient has been followed up for at least 5-years after her/his last study treatment, or earlier, if one of the following is documented for all treated patients: withdrawal of consent, loss to follow-up, or death. This is expected to take place approximately 8 years after the enrollment of the first patient, based on an expected 18-month recruitment period per cohort, 12 months of study treatment, and 5 years of follow-up after the last study treatment

Patients' satisfaction with trastuzumab SC administration using the SID (**Cohort B** patients who went on to self-administration only) will be summarized by frequency tables and presented graphically.

6.5.3 Other Analyses

Baseline characteristics will be summarized overall and for each treatment cohort. The demographic profile, medical history, HER2-positivity, and serum pregnancy test at screening will be listed and summarized using appropriate descriptive statistics: mean, standard, median, range (minimum and maximum), and 25th–75th quartiles for the continues variables and number/percentage of patients, medians, and ranges for the categorical variables.

Concomitant medications will be summarized by class and preferred term for the ITT and safety populations. Within each cohort, the number of cycles, as well as dosing information (e.g., dose interruptions, modifications, and delays), will be summarized by median and range.

More details about the planned analyses will be presented in the SAP.

6.6 ANALYSIS POPULATIONS

The Safety Population (SP) will include all enrolled patients who received at least one dose of study medication. There will be two safety populations, one for each cohort (SP1 for **Cohort A** and SP2 for **Cohort B**).

The intent to treat (ITT) population will include all patients enrolled in the study.

The per-protocol population (PP) will include all ITT patients who have received at least one dose of study medication and did not have major protocol violations (which will be defined in the SAP).

6.7 PHARMACOKINETIC ANALYSES

Pharmacokinetic assessments will be limited to the confirmation of the presence and titer of trastuzumab in the serum of a subset of patients enrolled in **Cohort B** at select sites, who will also undergo immunogenicity testing (anti-trastuzumab assay; see Section 6.9.1).

6.8 PATIENT–REPORTED OUTCOME ANALYSES

Not applicable.

6.9 EXPLORATORY ANALYSES

6.9.1 Immunogenicity

Immunogenicity assessments will be summarized for a subset of patients enrolled in **Cohort B** at selected sites. The percentage of patients who develop anti-human antibodies (HAHAs and ADAs) to trastuzumab SC or rHuPH20 or both will be presented. Serum trastuzumab concentration data will be used for the evaluation of the anti-trastuzumab assay.

Details about analysis methods are provided in the Statistical Analysis Plan (SAP).

6.9.2 Observation Time

Exploratory study analyses for all clinical AEs that occur during the observation period will be evaluated, analyzed, and presented, and further exploratory analysis will be performed for all patients in **Cohort B** (within 6 hours after start of the first trastuzumab administration or within 2 hours after start of following trastuzumab administrations). Details of the analysis will be documented in the Statistical Analysis Plan (SAP) and will include the following:

- Analysis of frequency, incidence, and grade of AEs during the observation period
- Analysis of time from last preceding administration of study drug to onset time of AE occurrence (dd:mm:yyyy:hh:mm) during the observation period
- Analysis of time to resolution (dd:mm:yyyy:hh:mm) and outcome of AEs observed during the observation period
- Analysis of treatments provided following AEs during the observation period

Exploratory analyses on the usability of the SID summarizing the parameters collected via SID monitoring questionnaire (Appendix 7) will be provided to the first 48 patients enrolled in **Cohort B** who were judged able, and were willing to self-administer remaining doses from the SID under direct observation of the HCP. The SID Device Observation is to be completed by HCPs.

6.9.3 Subgroup Analyses

Selected safety and efficacy summaries will be repeated for the subgroup of patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low-risk,

node-negative tumors ≤ 1.0 cm, elderly patients (> 65 years of age), or patients who refuse chemotherapy. Enrollment of patients treated without chemotherapy will be limited to ≤ 10% of the total study population. Details of the planned subgroup analyses will be provided in the SAP.

6.10 INTERIM SAFETY ANALYSES

Three interim safety analyses are planned when approximately 500, 1000, and 2500 patients have received at least one trastuzumab SC injection.

Details regarding the planned interim safety analyses will be provided in the Steering Committee Charter.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Roche will supply electronic eCRF specifications for the study. The overall procedures for quality assurance of clinical study data are described in the Roche Standard Operational Procedures and/or those of the global Contract Research Organization (CRO) designee.

Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

The responsible monitors (CRO designee) will visit the investigators and will be allowed, on request, to inspect the study records, provided that patient confidentiality is maintained in accordance with local requirements. It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor must verify that the patient received the study drug as prescribed in the protocol. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the eCRF. The investigator (or deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

Roche will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically

transferred electronically from the CRO to Roche, and Roche's standard procedures will be used to handle and process the electronic transfer of these data.

For classification purposes, preferred terms will be assigned by the Sponsor (or CRO designee) to the original terms entered on the eCRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for adverse events and diseases and the International Non-proprietary Name (INN) Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

7.2 ELECTRONIC CASE REPORT FORMS

A global CRO will handle eCRF development and review, eCRF online monitoring/data management, statistics, preparation of the final statistical report and clinical study report (CSR). The CSR will be prepared when all patients have completed the Safety Follow-up visit (4 weeks after the last dose of study treatment). An addendum to the CSR will be prepared when the last patient has completed 5 years of post-treatment follow-up.

An eCRF must be completed for each enrolled (registered) patient. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. All eCRFs should be completed by designated, trained site staff, who will transcribe the collected patient data from paper source documents onto the eCRF. In no case is the eCRF to be considered as source data for this trial. eCRFs should be reviewed and electronically signed and dated by the investigator or an authorized designee. eCRFs will be submitted electronically to Roche and should be handled in accordance with instructions from Roche.

An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. The data will be transferred directly to the clinical database.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc will be required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered by authorized site personnel from source documents into the eCRFs are accurate.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the accuracy of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and EC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of Roche. Written notification should be provided to Roche prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

Roche's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Roche or its designee must review and approve any proposed deviations from Roche's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before EC submission. The final EC–approved Consent Forms must be provided to Roche for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised EC-approved Consent Forms must be provided to Roche for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the EC by the Principal Investigator and reviewed and approved by the EC before the study is initiated.
In addition, any patient recruitment materials must be approved by the EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC. Investigators are also responsible for promptly informing the EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and EC. Investigators may receive written safety reports or other safety-related communications from Roche. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Roche maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Roche location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the national and local health authorities, Roche monitors, representatives, and collaborators, and the EC for each study site, as appropriate

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 SITE INSPECTIONS

Site visits will be conducted by Roche or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Roche monitors, representatives, and collaborators; and the ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

Please refer to the separate contact list for the contact information of the Sponsor and Global Roche Study Personnel.

This information can be found at the local Roche affiliate office, and within the Investigator Site File.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

Roche will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Investigators are responsible for promptly informing the EC of any amendments to the protocol.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

	Screening	Study Treatment 3-weekly (18 cycles)				Safety Follow-Up Visit [q,r]	Follow-Up Visits [k,r]
Study Week (Treatment Cycle #)	**Day -28 to 1**	**Week 1 to 22 Cycles 1 to 8 [r,u]**	**Week 25 Cycle 9 [r]**	**Week 28 to 49 Cycles 10 to 17 [r]**	**Week 52 Cycle 18 [r]**	**4 weeks After Last Study Treatment**	**(Minimum 5 years After Last Study Treatment)**
Explain study and obtain signed Informed Consent [a]	x						
Demographic profile [b] and medical history	x						
HER2 Determination	x						
Review inclusion/exclusion criteria	x						
Physical Exam [c]	x	Approximately 3-monthly (every 4 cycles) [p]				x	x [k]
Weight, height [d]	x		x [d]				x [d]
Vital Signs [e]	x	Approximately 3-monthly (every 4 cycles) [e]				x	
ECOG performance status	x	Approximately 3-monthly (every 4 cycles) [p]				x	
Cardiac monitoring		Approximately 3-monthly (every 4 cycles) [p]				x [s]	Cardiac assessments at 6, 12 and 24 months, and at 3, 4 and 5 years following treatment cessation
12-lead ECG	x						
LVEF [f]	x [f]						
Signs/symptoms	x						
Pregnancy test [g]	x	As clinically indicated					

Appendix 1 Schedule of Assessments (cont.)

	Screening	Study Treatment 3-weekly (18 cycles)				Safety Follow-Up Visit [q,r]	Follow-Up Visits [k,r]
Study Week (Treatment Cycle #)	**Day -28 to 1**	**Week 1 to 22 Cycles 1 to 8 [r,u]**	**Week 25 Cycle 9 [r]**	**Week 28 to 49 Cycles 10 to 17 [r]**	**Week 52 Cycle 18 [r]**	**4 weeks After Last Study Treatment**	**(Minimum 5 years After Last Study Treatment)**
Blood samples for immunogenicity and PK testing [h]	x [h]		x [h]				x (6 months after last study treatment)
Hematology and biochemistry [i]	x [t]		x		x	x	
Imaging scan to exclude residual/recurrent disease [j]	x						
Routine Breast-cancer follow-up [k]		Assessments as per institutional practice or ASCO adjuvant follow-up guidelines 2006 to be reported 6-monthly [k]					
AEs and SAEs [l]	x	x	x	x	x	x	x
Concomitant medication [m]	x	x	x	x	x	x	x [m]
Trastuzumab SC [n]		x	x	x	x		
Exploratory Observation Time [v]		x	x	x	x		
SID monitoring questionnaire [w]		x	x	x	x		
Treatment compliance		x	x	x	x		
SID satisfaction questionnaire [o]		After Cycle 4 [o]				x	
Survival		x	x	x	x	x	x (at *12,* 24 months and at 3, 4, and 5 years after last treatment)

Note: First dose of study drug = study Cycle 1, Day 1.

[a] Written Informed Consent must be obtained before any study-specific assessments or procedures are performed.

Appendix 1 Schedule of Assessments (cont.)

[b] Demographic data include date of birth, gender, and self-reported ethnic origin.

[c] General physical exam may include neurological exam, as clinically indicated.

[d] Weight is measured for all patients at screening. For patient participating in PK sampling at Cycle 9 and 6 month after last study treatment. Height is only measured at screening.

[e] Vital signs include blood pressure, heart rate measurement and temperature at screening and Safety Follow-up visit, as well as pre- and immediately post-trastuzumab SC administration at Cycles 1, 5, 9, 13, and 18.

[f] LVEF has to be assessed within 14 days prior to the first study treatment for anthracycline regimens or 28 days prior to the first study treatment for anthracycline-free regimens, and 3-monthly thereafter by ECHO, MUGA, or MRI. The same imaging technique needs to be used per patient throughout the study. A further LVEF assessment will be performed if patients are symptomatic at an LVEF between 45%–49% and a drop ≥ 10% as clinically indicated, but within 3 weeks. LVEF at the Safety Follow-up visit (4 weeks after the end of treatment) is not mandatory but will be performed if clinically indicated.

[g] Applicable to women of childbearing potential; a serum pregnancy test needs to be completed within 7 days prior to the first study treatment. Subsequent pregnancy testing should be completed as clinically indicated for the duration of study treatment and until at least 7 months after the last dose of study treatment. Any positive urine pregnancy test needs to be confirmed by serum pregnancy test.

[h] Subset of **Cohort B** selected sites only: Blood samples (4 mL for PK and anti-trastuzumab analysis and 2 mL for rHuPH20 antibody analysis) should be taken at baseline (after eligibility is confirmed, i.e., just before the first study treatment) pre-Cycle 9 dose and 6 months after the last dose of study treatment.

[i] Hematology: hemoglobin, WBC and differential, absolute neutrophil count (ANC), platelet count. Biochemistry: creatinine, urea (BUN), SGPT (ALT), SGOT (AST), total bilirubin, alkaline phosphatase, albumin, sodium, potassium, and calcium. Additional hematology and biochemistry tests may be performed as per institutional practice, but these data will not be collected. On Day 1 of Cycles 9 (Week 25) and 18 (Week 52), samples will be taken predose, and the results will be reviewed prior to dosing.

[j] Screening radiologic examinations to exclude metastatic disease should include a bilateral mammogram or breast MRI and chest X-ray (CXR). These imaging tests do not need to be repeated if completed within 12 months prior to the first study treatment. In addition, bone scan, liver imaging, and brain CT scan should be performed if clinically indicated.

[k] American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006). In brief:

History/physical examination: every 3–6 months for the first 3 years after primary therapy, every 6–12 months for years 4 and 5, then annually.

Mammography: first post-treatment mammogram 1 year after the initial mammogram that leads to diagnosis, but no earlier than 6 months after definitive radiation therapy. Subsequent mammograms should be obtained as indicated for surveillance of abnormalities.

Pelvic examination: regular gynecologic follow-up is recommended for all women. Patients who receive tamoxifen should be advised to report any vaginal bleeding to their physicians.

The following are not recommended for routine surveillance: Routine blood tests (full blood counts and liver function tests), imaging studies (chest x-ray, bone scans, liver ultrasound, CT scans, FDG-PET scans, and breast MRI), tumor marker assessments (CA 15-3, CA 27.29, and CEA).

Appendix 1 Schedule of Assessments (cont.)

[l] After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected. All treatment-emergent AEs occurring until 4 weeks after the last administration of trastuzumab SC will be recorded in the eCRF, irrespective of the type of event and drug-event relationship. From 4 weeks after the last study drug administration until the end of the follow-up period, related AEs, related/unrelated SAEs, and cardiac AEs should be reported.

[m] All concomitant medication will be recorded between the Screening and the Safety Follow-up visits. Thereafter, only breast cancer treatments (e.g., *endocrine* therapy), anti-cancer treatments given to treat a recurrence, *and* medications related to the treatment of *SAEs will be recorded.*

[n] Trastuzumab SC is administered subcutaneously in the upper thigh at a fixed dose of 600 mg, 3-weekly for a total of 18 cycles.

[o] After the 4th cycle and at their final study visit (at least 1 day after the last trastuzumab SC injection), patients in **Cohort B**, who have successfully completed a minimum of 2 self-administrations of the study drug, will be asked to assess their satisfaction with the administration of trastuzumab SC using the SID by completing the 5-item SI satisfaction questionnaire.

[p] Approximately 3-monthly (every 4 cycles) refers to pre-dosing at: Week 13/Cycle 5, Week 25/Cycle 9, Week 37/Cycle 13, and Week 52/Cycle 18.

[q] Patients will undergo a Safety Follow-up visit 4 weeks after their last dose of study treatment.

[r] Visit windows of ± 3 days allowed for all visits (Cycles 1 to 18), ± 5 days at Safety Follow-up visit, and ± 15 days allowed for Follow-up visits.

[s] An LVEF is only required at the Safety Follow-up visit if clinically indicated.

[t] Screening laboratory values should be used to confirm eligibility.

[u] For patients initiated on trastuzumab SC in neoadjuvant setting, surgery should be scheduled after dosing at Cycle 8. Pathologist post-surgery tumor assessment should be recorded.

[v] **Cohort B** only, observation time (6 hours post start of the first administration trastuzumab and 2 hours after the start of subsequent administrations) will include, in addition to onset and resolution dates and times of AEs, the collection of detailed information about premedications prior to trastuzumab administration and, in addition to the date, the onset and resolution time of treatment of AEs occurring during the observation time is investigated.

[w] For SID monitoring purposes, the first 48 patients enrolled in **Cohort B** will have their SID use monitored and recorded on the SID monitoring questionnaire by the trained HCP or investigator intended to collect information about aspects of use related to usability of the device.

Appendix 2
ECOG Performance Status Scale

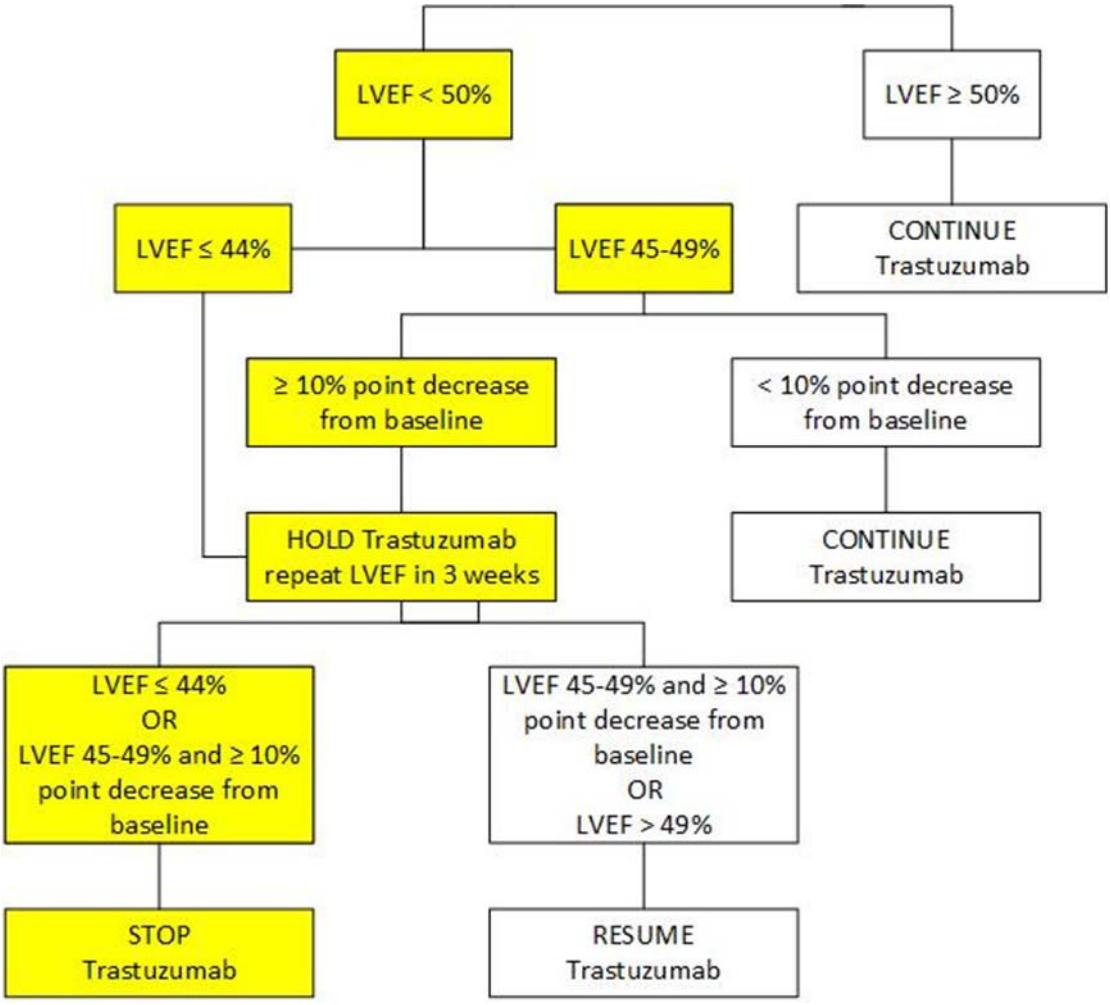
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

Source: Oken M et al. 1982.

Appendix 3
New York Heart Association (NYHA) Functional Classification System for Heart Failure

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Appendix 4
Algorithm for Continuation and Discontinuation of Trastuzumab SC Based on LVEF Assessment in Asymptomatic Patients



Appendix 5
Common Terminology Criteria for Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health, National Cancer Institute

The CTCAE v4.0 manual can be found at the following URL:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix 6
Single-Use Injection Device (SID) Satisfaction Questionnaire

The SID satisfaction questionnaire is to be completed by patients in **Cohort B** who completed a minimum of 2 (preferably 3) self-administrations of the study drug.

Please rate your level of agreement or disagreement with each the following statements, by placing an "X" in the appropriate box (one answer for each statement):

1. **Following the first injection given by the physician/nurse and training on how to use the SID, I felt comfortable injecting the study drug by myself.**

☐$_1$ Strongly Disagree ☐$_2$ Disagree ☐$_3$ Unsure ☐$_4$ Agree ☐$_5$ Strongly agree

2. **The SID was convenient and easy to use.**

☐$_1$ Strongly Disagree ☐$_2$ Disagree ☐$_3$ Unsure ☐$_4$ Agree ☐$_5$ Strongly agree

3. **I am confident giving myself an injection in the thigh with the SID.**

☐$_1$ Strongly Disagree ☐$_2$ Disagree ☐$_3$ Unsure ☐$_4$ Agree ☐$_5$ Strongly agree

4. **Taking all things into account, I find self-administration using the SID satisfactory.**

☐$_1$ Strongly Disagree ☐$_2$ Disagree ☐$_3$ Unsure ☐$_4$ Agree ☐$_5$ Strongly agree

5. **If given the opportunity, I would choose to continue self-injecting the study drug using the SID in the future.**

☐$_1$ Strongly Disagree ☐$_2$ Disagree ☐$_3$ Unsure ☐$_4$ Agree ☐$_5$ Strongly agree

Appendix 7
Single-Use Injection Device (SID) Observers Usability Questionnaire

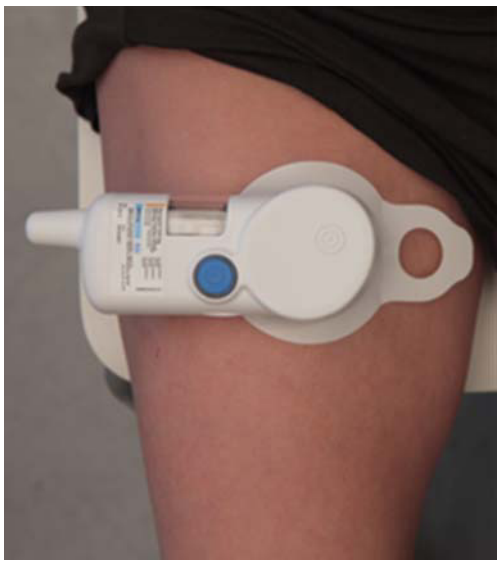
The SID Device Observation is to be completed by HCPs (physician or nurses) for 48 patients selected in **Cohort B** who were judged able, and were willing to self-administer remaining doses from the SID under direct observation of the HCP. Patients participating in the usability questionnaire must self-administer with the SID and no assistance is to be provided unless it was not possible for a user to use the SID correctly (in which case assistance is permitted). In this instance, the SID usability questionnaire must still be completed.

Positioning of device; body site selection and prepare skin

1. Does selection of body positioning of SID comply with instruction (semi-supine, anterior thigh)?
   (Circle the applicable answer) **[YES] [NO]**
   If NO please comment:
   _____
   _____
   _____

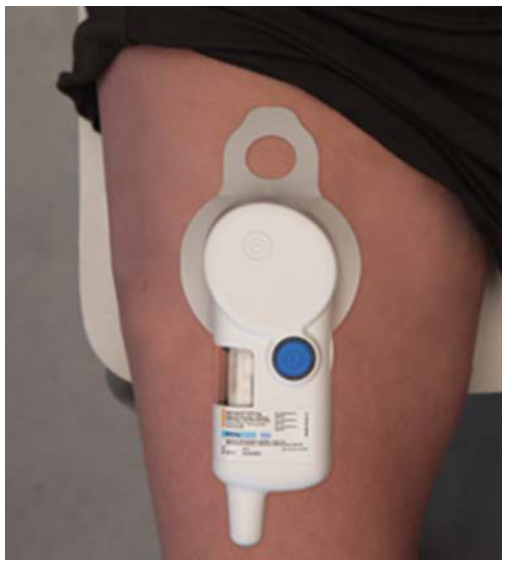
2. Which image below best describes the placement of the SID on the thigh of the patient? *(Circle the applicable answer)*.

[A]



[A] Across the Thigh

[B]



[B] Along the thigh

Appendix 7 Single-Use Injection Device (SID) Observers Usability Questionnaire (cont.)

3.	Was the body site dry before attaching the SID? *(Circle the applicable answer)*	**[YES]**	**[NO]**
4.	Was the SID stuck onto the skin with the adhesive pad removed? *(Circle the applicable answer)* If NO please comment: _____ _____	**[YES]**	**[NO]**
5.	**Was the full dose injected from the SID?** Piston at end position of cartridge at the end of injection. *(Circle the applicable answer)* If NO please comment: _____ _____	**[YES]**	**[NO]**
6.	**Did the SID stop at any time during administration?** This is indicated by the motor stopping and indicator light flashing alternating green and orange. *(Circle the applicable answer)* If YES please comment: _____ _____	**[YES]**	**[NO]**
7.	**IF the SID did stop during the administration** - **Was the problem corrected to resume delivery?** (To correct the SID was depressed onto the skin again within 10 seconds and pressure maintained until the status light resumed slowly flashing orange and injection continued).	**[YES]**	**[NO]**
8.	Following completion of the injection and removal of the SID from the body: **Did the needle automatically retract into SID?**	**[YES]**	**[NO]**
9.	Was there residual liquid left at the injection site? If **Yes**, please tick **one** of the options below: **1 to 5 drops [ ]** **More than 5 drops [ ]**	**[YES]**	**[NO]**

Appendix 7 Single-Use Injection Device (SID) Observers Usability Questionnaire (cont.)

10. Was assistance given to a user at any time during the self-administration? **[YES]** **[NO]**
    If YES please comment:
    _____
    _____
    _____
    _____
    _____
    _____

TITLE:	**GLOBAL ENHANCED PHARMACOVIGILANCE (PV) PREGNANCY PROGRAM**
VERSION NUMBER:	2.0
PRODUCT:	Herceptin® (trastuzumab; RO0452317)
SAFETY RESPONSIBLE :	[redacted], M.D.
EPIDEMIOLOGIST:	[redacted] M.P.H.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

FINAL APPROVAL

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ARISg	Roche Global Safety Database
CDS	Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
DSC	Drug Safety Committee
EBC	Early breast cancer
EEA	European Economic Area
EMA	European Medicines Agency
eRMP	European Risk Management Plan
EU	European Union
GD	Gestation day
GQ	Guided Questionnaire
HCP	Healthcare Provider
HER2	Human Epidermal Growth Factor Receptor 2
MAP	Market Access Programs
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non Interventional Study
PV	Pharmacovigilance
SAE	Serious adverse event
SEER	Surveillance, epidemiology and end results
SmPC	Summary of Product Characteristics
US	United Stated of America

1. BACKGROUND

As a post-approval measure for Perjeta (pertuzumab) the EMA requested to set up a Global Enhanced Pharmacovigilance (ePV) Pregnancy Program.The FDA imposed a similar post-approval measure by requesting to implement a Global Enhanced Pharmacovigilance Pregnancy Program for the HER2 franchise (Herceptin, Perjeta, Kadcyla), also considering the low enrollment in the ongoing MotHER registry for the three products.

The Global Enhanced Pharmacovigilance (PV) Pregnancy Program is listed in the Herceptin Risk Management Plan (RMP) as a planned action to address the important identified risk of oligohydramnios.

1.1 HERCEPTIN® (TRASTUZUMAB)

Herceptin is a recombinant humanized anti-p185 HER2 monoclonal antibody that binds specifically and with high affinity to the extracellular domain of the HER2 receptor. Herceptin has been shown to inhibit the proliferation of human tumor cells overexpressing HER2 both in vitro and in vivo.

As per CDS v 16.0, Herceptin is indicated for the treatment of

- Patients with MBC whose tumors overexpress the HER2 protein as monotherapy in patients who have received prior chemotherapy, in combination with an aromatase inhibitor, and in combination with chemotherapy for patients who have not previously received chemotherapy
- Patients with HER2-overexpressing operable early breast cancer (EBC) following surgery, chemotherapy (neoadjuvant plus adjuvant or adjuvant only), and radiotherapy (if applicable), in combination with taxane-based chemotherapy following adjuvant chemotherapy with anthracycline plus cyclophosphamide, in combination with docetaxel-carboplatin chemotherapy, and in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) breast cancer or tumors > 2 cm in diameter
- Patients with HER2-overexpressing metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

1.1.1 Preclinical Findings and Oligohydramnios as an Important Identified Risk for Herceptin

Reproductive toxicity studies conducted in female Cynomolgus monkeys given Herceptin as daily IV injections for 4 days followed by twice weekly administration for the duration of the dosing period revealed no alterations in menstrual cycle or sex hormone profiles and no Herceptin related embryotoxicity or effects on foetal development. Embryotoxicity studies in monkeys have demonstrated placental transfer of Herceptin to the foetus, as confirmed by the detection of Herceptin in foetal serum. Compared with serum concentrations, Herceptin was detected at relatively low levels in the milk of lactating

monkeys. Herceptin detected in the milk of lactating monkeys had no effect on neonatal growth and development from birth to one month of age, when monitoring was discontinued.

However, when assessing the risk of reproductive toxicity to humans, it was also important to consider the significance of the rodent form of the HER-2 receptor in normal embryonic development, and the embryonic death in mutant mice lacking this receptor. Placental transfer of Herceptin was observed during the early and late days of gestation of the foetal development period (days 20 to 50 and days 120 to 150, respectively).

In the post-marketing setting cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin.

The non-clinical program revealed no direct toxicity of Herceptin via the intravenous, subcutaneous or intrathecal route (developmental toxicity has been identified as an important potential risk for Perjeta, based on non-clinical findings).

1.2 PERJETA (PERTUZUMAB)

Perjeta (rhuMAb 2C4) is a recombinant, humanized, immunoglobulin (Ig)G1κ, monoclonal, anti-human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2) antibody. It is the first in a new class of targeted cancer treatments called HER2 dimerization inhibitors. By binding to the subdomain 2 epitope of the extracellular domain of HER2, it prevents hetero-dimerization of HER2 with other members of the HER family (HER1, HER3 and HER4). As a result, ligand-activated downstream signaling is blocked by pertuzumab. Perjeta is also capable of activating antibody-dependent cell-mediated cytotoxicity (ADCC). It has, thus, a unique, distinct, and complementary mechanism of action from existing HER2-targeting therapies, such as Herceptin. Perjeta contains the same Fc region as Herceptin, but differs from the latter in the epitope-binding regions of the light and heavy chains, which comprise the complementarity determining regions of the antibodies. Consequently, although both Perjeta and Herceptin target the extracellular domain of HER2, they bind to distinct and non-overlapping regions of the receptor.

Perjeta is presently approved for use in combination with Herceptin® and Docetaxel for the treatment of patients with HER2-positive metastatic breast cancer (MBC) and in the US for neoadjuvant treatment for locally advanced, inflammatory or early breast cancer in combination with Herceptin and docetaxel as part of a fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin containing treatment regimen. Currently, Perjeta is being investigated in other indications by Roche. Clinical trials in early breast cancer, gastric cancer and ovarian cancer are ongoing to further investigate the use of Perjeta and Herceptin in combination with a variety of chemotherapeutic agents.

1.2.1 Preclinical Findings and Oligohydramnios as an Important Potential Risk for Perjeta

Based on non-clinical findings, developmental toxicity has been identified as an important potential risk for Perjeta. Placental transfer of Perjeta was confirmed in

cynomolgus monkeys. Foetal to maternal Perjeta serum concentration ratios were similar across a 10-fold range of doses at clinically relevant concentrations (20-fold greater than human clinical dose). Perjeta-related embryo-foetal lethality, oligohydramnios, and microscopic evidence of delayed renal development occurred in a study when Perjeta was administered intravenously from Gestation Day 19 (GD19) through GD50 to pregnant cynomolgus monkeys, the period of organogenesis in this species (GD20−50). In addition, consistent with foetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 at 30 mg/kg and 1 of 2 at 100 mg/kg), ventricular septal defects (1 of 6 at 30 mg/kg), thin ventricular wall (1 of 2 at 100 mg/kg) and minor skeletal defects (external - 3 of 6 at 30 mg/kg) were also noted. Systemic maternal and foetal exposure at clinically relevant Perjeta concentrations was confirmed.

No foetal studies in humans have been performed, and pregnant or lactating women have been excluded from all Perjeta trials.

1.3 USE OF HERCEPTIN DURING PREGNANCY AND LACTATION

No foetal studies of Herceptin in humans have been performed.

Professional labeling documents indicate that Herceptin should be avoided during pregnancy, unless the potential benefit for the mother outweighs the potential risk to the foetus. In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin.

Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for 7 months after treatment has concluded. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with Herceptin or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable. It is not known whether Herceptin can affect reproductive capacity.

It is not known whether Herceptin is secreted in human milk. As human immunoglobulin G (IgG) is secreted into human milk, and the potential for harm to the infant is unknown, breast-feeding should be avoided during Herceptin therapy.

Most, if not all, cancer therapeutics are considered harmful to the embryo/foetus and it is common medical practice to strongly advise patients not to become pregnant during treatment for breast cancer to protect the mother (due to concern that pregnancy hormones might have a detrimental effect on breast cancer outcomes) and to avoid harm to the embryo or foetus.

1.4 ESTIMATE OF HERCEPTIN-EXPOSED PREGNANCIES GLOBALLY

The MAH estimates that worldwide, a maximum of 645 pregnancies might occur each year in patients exposed to Herceptin. These estimates are based on the following assumptions:

Approximately 1,383,500 women will be diagnosed annually with breast cancer worldwide (Jemal et al, 2011). (Note: Herceptin is not currently approved in all countries; however, the following major markets of United States, European Union, Canada and Japan account for ~42% of breast cancer cases)

Amplification and/or overexpression of HER2 occurs in approximately 15% to 20% of breast cancers (Wolff et al, 2007 [ref4]; Chia et al, 2008 [ref5]; Ross et al, 2009 [ref6]), suggesting around 240,000 cases of HER2-positive breast cancer per year globally (based on incidence figures for breast cancer).

Among HER2-positive breast cancer patients (any stage), ~28% of women are less than 50 years of age (SEER 2013), i.e., of an age that is considered to be of child-bearing potential (<67,200 patients per year globally).

It is estimated that ~90% of all patients with HER2-positive breast cancer will receive Herceptin (data available upon request), resulting in <60,480 Herceptin-treated patients of child-bearing age.

Approximately 1.0% of these women may become pregnant, based on an analysis of pregnancies in Herceptin-treated patients with breast cancer (including patients treated in both the adjuvant and metastatic setting) who are < 50 years of age from a large US insurance claims database (internal analysis, available upon request). Therefore, conservatively, a maximum of 605 pregnancies per year might be expected among breast cancer patients treated with Herceptin globally.

The estimated number of women with advanced stage gastric and gastro-esophageal junction (GEJ) cancer treated with Herceptin and who may become pregnant is small because gastric/GEJ cancers are more commonly diagnosed in men and at older ages.

Approximately 349,000 women will be diagnosed annually with gastric/GEJ cancer worldwide (Jemal et al, 2011). Note: China, all of Europe, Japan and the US and Canada account for 38%, 17%, 10.6% and 2.8% of gastric cancer cases respectively (Ferlay et al, 2013).

Of these, 33% or 115,000 cases are expected to be advanced or metastatic stage disease (Howlander et al, 2014).

Amplification and/or overexpression of HER2 occur in approximately 20% of gastric/GEJ cancers (Van Custem et al, 2014), suggesting around 23,000 cases of HER2-positive gastric/GEJ cancer per year globally.

Among these HER2-positive gastric/GEJ cancer patients, ~17% (~3,900 cases) are less than 50 years of age (SEER 2014) and considered to be of child-bearing potential.

Even if we assume that all 3,900 patients are also treated with Herceptin and then 1% of these women would become pregnant, we would expect only ~40 pregnancies per year among advanced stage gastric/GEJ cancer patients treated with Herceptin globally.

These are extremely conservative estimates (605 pregnancies for breast cancer and 40 pregnancies for gastric/GEJ cancer) as patients receiving Herceptin treatment are warned about the potential fetal harm and are advised to use effective contraception during treatment and for 7 months following the last dose of Herceptin. In addition, considering that the spontaneous reports are typically underreported in the post-marketing setting, the expected number of reported pregnancies is very low (Hazell et al, 2006).

2. GLOBAL ENHANCED PV PREGNANCY PROGRAM

2.1 RATIONALE

The Global Enhanced Pharmacovigilance (PV) Pregnancy Program was designed to monitor the pregnancy period and the outcome of any potential pregnancy occurring during and within seven months after the use of last dose of Herceptin (IV and SC formulation) for any indication. A global PV program will enable Roche to collect and assess information on the pregnancy period as well as pregnancy outcomes. As outlined in section 1.4 only a few patients are expected to become pregnant while receiving Herceptin treatment in the metastatic breast cancer setting. The global ePV pregnancy program will collect data for Herceptin use in all indications (Early and Metastatic Breast Cancer and Advanced Gastric Cancer).

Roche commits to investigate any reports of Herceptin-exposed pregnancies received, i.e. pregnancies occurring during the use of Herceptin and within seven months after exposure to Herceptin, and to follow-up infants for the first year of life.

The same program has been developed for pertuzumab (Perjeta®) and trastuzumab emtansine (Kadcyla®). However, due to a slightly longer half-life, a trastuzumab-/trastuzumab emtansine-exposed pregnancy is defined as a pregnancy that occurs in a female patient actively taking trastuzumab/trastuzumab emtansine or within seven months after stopping treatment with trastuzumab-/trastuzumab emtansine, compared to six months with pertuzumab.

2.2 OBJECTIVES

The objective of the program is to collect additional information on women exposed to Herceptin during pregnancy or within seven months after last Herceptin dose in order to better assess and describe potential adverse pregnancy complications (e.g. oligohydramnios), pregnancy outcomes (i.e. live birth, ectopic pregnancy, embryo-foetal death, spontaneous or therapeutic abortions) and foetal/infant outcomes (e.g. major malformations, deformations, and functional deficits) among women treated with Herceptin during pregnancy or within seven months prior to conception. This will enable Roche to better understand the safety of Herceptin and to provide appropriate information to Healthcare Providers (HCPs), patients and Health Authorities.

2.3 DESCRIPTION

The Global Enhanced PV Pregnancy Program will be based on existing reporting mechanisms, coupled with enhanced follow-up of pregnancies and collection of data on infant outcomes. The program will be applied to reported pregnancies globally. These reports may be received from all the sources (details see section 3.1.1).

A Herceptin-exposed pregnancy is defined as the occurrence of pregnancy in a female patient actively taking Herceptin or within seven months after stopping treatment with Herceptin.

Key data elements needed to assess risks to the mother and child associated with exposure to Herceptin will be collected for the program in a centralized Roche Global Safety Database (ARISg), including, but not limited to:

- Collection of pregnancy information, obstetric history (e.g. date of last menstrual period, estimated date of delivery, number and outcomes of prior pregnancies) and medical history for all Herceptin pregnancy reports
- Collection of Herceptin, concomitant Perjeta and chemotherapy exposure status (including start and stop dates, route of administration, and dosage) for each reported pregnancy
- Collection of a description of adverse pregnancy complications (e.g. oligohydramnios) with results of relevant laboratory tests or procedures
- Collection of information on the outcome of each Herceptin-exposed pregnancy (i.e. live birth, stillbirth, ectopic pregnancy, spontaneous or therapeutic abortion) with results of relevant laboratory tests or procedures
- Collection of foetal and infant outcomes for each Herceptin-exposed pregnancy (e.g. normal baby, malformations, deformations, etc.) and follow-up at 3, 6 and 12 months of life

Roche Drug Safety will ensure a consistent global approach for capturing all pregnancy and foetus/infant-related information via the standard Roche Pregnancy Report Form If a fetal abnormality during pregnancy or any malformation within the first year of the infant's life is reported via a standard Roche Pregnancy Report Form, a Guided Questionnaire (GQ) will be sent out to capture additional targeted information, particularly on the events of oligohydramnios, fetal renal abnormalities, intrauterine growth retardation and birth defects..

Efforts will be made to raise awareness of the Global Enhanced PV Pregnancy Program and to increase spontaneous reporting of all pregnancies (including pregnancies with normal outcomes), (see Section 4 Communication Plan).

Any signal arising from the program will be discussed in the PBRER/PSUR.

3. DESIGN OF THE PROGRAM

3.1 DATA COLLECTION

The Global Enhanced PV Pregnancy Program will include both, retrospective pregnancy reports (i.e. when the pregnancy outcome is known prior to reporting of the pregnancy to Roche) and prospective pregnancy reports (i.e. when the pregnancy outcome is not known prior to reporting of the pregnancy to Roche). All reports of pregnancy will be entered into the Roche Global Safety Database.

3.1.1 Sources of Information

Pregnancy reports may be received from any of the following:

- Roche-sponsored clinical trials

- Investigator-sponsored trials supported by Roche
- Roche-sponsored registries
- Spontaneous reports
- NIS/MAP
- Literature reports
- Regulatory authority reports
- Roche employees

Note: The Roche Safety Data Exchange Agreements ensures that all investigator-sponsored trials supported by Roche adhere to the pharmacovigilance standard operating procedures.

Roche will follow up with the authors of literature reports and/or editors of the publication in order to obtain required information on any Herceptin-exposed pregnancy.

3.1.2 Pregnancy Information

Initial information will be reported to Roche by the standard Roche Pregnancy Report Form and should include the following information:

1. Reporter information
2. Exposed parent's details
3. Product information (Exposure to Herceptin and concomitant medications, including Perjeta and chemotherapy [start and stop dates, route of administration, dosage])
4. Medical history/risk factors (including diabetes, infections, allergies, smoking, alcohol use, illegal drug use) and Contraception used
5. Obstetric history (previous pregnancies with pregnancy and foetal/infant outcomes)
6. Pregnancy information (e.g., date of last menstrual period, estimated date of delivery etc.)
7. Pregnancy outcome
8. Relevant laboratory tests/procedures pre and post outcome (e.g. amniocentesis, ultrasound etc.)

At the end of the second trimester (24-26 weeks of gestation), further information on a standard Roche Pregnancy Report Form will be requested, including the following:

- New information on the progress of the pregnancy
- Results of any new laboratory test or procedures
- Any other relevant information

3.1.3 Pregnancy Outcome Information

Two weeks after the expected date of delivery, further information will be requested via the standard Roche Pregnancy Report Form, including details on the following:

- Relevant laboratory tests/procedures pre and post outcome (e.g., amniocentesis, ultrasound)
- Mode of delivery
- Birth outcome
- Infant information
- Relevant laboratory tests/procedures for baby/foetus
- Additional information

For any congenital abnormality, the reporter will be asked to complete a Serious Adverse Event (SAE) form and a Guided Questionnaire.

3.1.4 Infant Follow-up Information

At 3, 6 and 12 months of life, further information will be requested using the standard Roche Pregnancy Report Form to provide updates on the following:

- Malformations/deformations diagnosed since the previous report
- Results of any relevant laboratory / diagnostic tests or procedures
- Additional information
- For any abnormality in the infant, the reporter will be asked to complete a Serious Adverse Event (SAE) form

In case there is an abnormality during pregnancy or malformation within the first year of the infant's life detected and reported via a standard Roche Pregnancy Report Form, a GQ will be sent out to the healthcare provider to capture additional targeted information.

A centralized tracker will be maintained by Roche Drug Safety Operations, which will trigger follow-up requests at the defined time points detailed above, and the dispatch of GQ if applicable (i.e. in case of a reported congenital abnormality or malformation). Reports of Herceptin-exposed pregnancies in clinical studies will be followed up via the SAE responsible by Roche Drug Safety Operations until pregnancy outcome information has been received (which was requested 14 days after the expected date of delivery). The infants will then be followed up by Roche Drug Safety Affiliates (as allowed by local legal and data protection requirements). Spontaneous reports of Herceptin-exposed pregnancies and infants will be followed up by Roche Drug Safety Affiliates (as allowed by local legal and data protection requirements). When additional methods of contact are provided and permissible in the country where the cases are reported, the Sponsor will attempt a second form of follow-up contact in order to minimize the loss to follow-up. For example, in the USA, a second form of contact for follow-up may be established by phone.

3.2 REPORT FORMS USED IN THE PROGRAM

The following forms will be used to collect information on pregnancies and pregnancy outcomes:

- Current version of a standard Roche Pregnancy Report Form (gcp_for000084 RO-GNE Pregnancy Report Form; SRD-0115311 Global: Clinical Trial Pregnancy Reporting Form)
- Guided Questionnaire (see Appendix 1)
- Authorization forms as mandated by local laws and regulations with regards to data protection (available at Roche Drug Safety Affiliates)

For all spontaneously reported pregnancies, Roche will make every attempt to identify all relevant HCPs (including the prescribing physician, gynecologist, neonatologist, and pediatrician), and all reports of pregnancies will be followed up via the HCPs, as appropriate. In the case of reports received from patients, the patient will be requested to provide contact details for relevant HCPs.

Relevant medical records may be requested by Roche, if necessary, from any HCP or institution providing care to the mother and/or infant.

All reports of pregnancies and/or infants received by Roche will be entered into the Roche Global Safety Database. Roche Drug Safety personnel or a designee will process the completed forms and will follow up with the reporter as described above. Each pregnancy case will be processed individually. Information on a normal baby will be integrated into the same pregnancy report. For infants with an abnormality, a separate SAE form will be completed, and a separate case from the mother pregnancy case will be created.

3.3 FREQUENCY AND DURATION OF FOLLOW-UP

In the event that follow-up requests are not responded to within 15 days, the standard Roche Pregnancy Report Form or GQ will be re-sent twice (after 15 and 30 days) by Roche Drug Safety Operations for clinical cases, or by Roche Drug Safety Affiliates for spontaneous cases as per the standard Roche query process for SAEs. When additional methods of contact are provided and permissible in the country where the cases are reported, the sponsor will attempt a secondary form of follow-up contact in order to minimize the loss to follow up. If a response to these requests is not received after 30 days, Roche Drug Safety Operations/Affiliates will document the loss to follow-up in the Roche Global Safety Database.

4. COMMUNICATION PLAN

To increase awareness of the Herceptin Global Enhanced PV Pregnancy Program amongst HCPs and patients

- All awareness materials directed at HCPs will display information about the risk of exposing an embryo or foetus to Herceptin, the importance of pregnancy prevention during Herceptin therapy and for seven months after the last dose of Herceptin, and instructions to report a known or suspected Herceptin-exposed pregnancy via the adverse event telephone numbers. Local implementation timelines are subject to local regulatory and legal rules.
- On the Herceptin website http://www.herceptin.com/ and local Herceptin websites globally, reference to the Global Enhanced PV Pregnancy Program and the need to report any potential Herceptin-exposed pregnancy via the adverse event telephone numbers will be made.

Within Roche, awareness will be raised on the Herceptin Global Enhanced PV Pregnancy Program by:

- Instructor led training for Roche personnel or designee responsible for receiving and triaging Herceptin reports on the enhanced PV measures and the need to solicit additional information on any Herceptin-exposed pregnancy and the infant during the first year of life.
- Awareness training for Roche staff or designee involved in the communication process.
- All clinical study protocols, in which Herceptin is used already, include instructions on pregnancy reporting.

5. ROUTINE PHARMACOVIGILANCE

In addition to pregnancy reporting described above, Roche vigilantly follows up on all Adverse Events (AEs) in patients exposed to Roche drugs in an attempt to ensure that complete details of the case are captured for optimal medical evaluation. This includes efforts to obtain all relevant information and to establish the final outcome of the AEs.

5.1 PERIODIC REPORTING

Any signal arising from the program will be discussed in the PBRER/PSUR.

The benefit/risk profile of Herceptin will also be re-evaluated on a periodic basis as part of the PSUR/PBRER.

6. DATA ANALYSIS

The most current Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding any reported congenital abnormality. Potential congenital abnormalities will be reviewed by appropriate experts within Roche. External specialists will be consulted if required.

6.1 SAFETY DATA MINING

All reports of Herceptin-exposed pregnancies will be captured in the Roche Global Safety Database.

To conduct safety signal detection activities, Roche is reviewing on a regular basis (at least monthly) the status of pregnancy reports for Herceptin. Validated monthly data searches of the Roche Global Safety Database are conducted by the Roche Data Management Group and the data are reviewed by the responsible Roche Drug Safety representative.

7. PROGRAM EVALUATION

7.1 METHODS TO ASSESS REPORTING RATE OF PREGNANCIES

Methods to assess whether Herceptin-exposed pregnancies are being reported will include routine monitoring activities such as review of published literature to assess whether additional pregnancies have been missed.

In addition, periodic analysis of the pregnancies occurring in patients receiving Herceptin conducted in U.S. medical claims database(s) is planned to assess the frequency of pregnancies in women treated with Herceptin in order to provide information on the expected number of pregnancies in the treated population. Although the complexity of pregnancy diagnosis codes may limit the accuracy and completeness of pregnancy data captured in medical claims databases, these data sources may be used to help inform on the effectiveness of the Global Enhanced PV Pregnancy Program in capturing Herceptin-exposed pregnancies in a given treated population. Any imbalance arising from this review will be discussed in the PBRER/PSUR.

7.2 METHODS TO ASSESS METHODOLOGY OF PV PROGRAM

Periodic tracking of the numbers of patients and infants and the extent of missing data per pregnancy reported (overall and for critical data elements such as Herceptin exposure and pregnancy outcomes) will be conducted. Appropriate efforts to modify the

data collection process will be made if excessive loss to follow-up or missing data for key data elements is found. Note that a similar pharmacovigilance evaluation process has been conducted in the industry for the collection and follow-up of pregnancy reporting for thalidomide with a high degree of success (Uhl et al. 2006 [ref9]; Bwire et al. 2011 [ref10]).

8. PROGRAM REPORTING

Any signal arising from the program will be discussed in the PBRER/PSUR.

The benefit-risk profile of Herceptin will be re-evaluated periodically and will be communicated as part of the PSUR/PBRER. Roche will inform relevant health authorities about any outcomes that may have a Public Health impact, as well as Roche's proposed actions in response to the new findings.

9. ADMINISTRATIVE STRUCTURE

Pregnancy reports will be reviewed by the Herceptin Safety Science Leader or designee, who in conjunction with the Herceptin Safety Team will provide reports on all safety-related issues, including pregnancies, to the Drug Safety Committee (DSC) as appropriate. The DSC is Roche's Governance Committee accountable for safety-related decisions. The benefit-risk relationship for Herceptin will be evaluated, and if necessary, a course of action and/or amendment to the Global Enhanced PV Pregnancy Program will be undertaken, as applicable. All subsequent amendments to the current Global Enhanced PV Pregnancy Program will be promptly communicated to relevant health authorities, as appropriate.

10. ETHICAL CONSIDERATIONS

10.1 CONFIDENTIALITY

Roche will maintain confidentiality standards by coding each patient captured by the Global Enhanced PV Pregnancy Program through assignment of a unique case identification number. Patient names will not be included in data sets that are transmitted to any Roche location.

Patient medical information obtained by the Global Enhanced PV Pregnancy Program is confidential and may only be disclosed to third parties if authorization is given by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by the Global Enhanced PV Pregnancy Program will be available for inspection upon request by representatives of the European Medicines Agency (EMA), the U.S. FDA and other national and local health authorities, as appropriate.

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Appendix 1
Guided Questionnaire: Pregnancy-related Adverse Events

GQ_Pregnancy
Related Adverse Event

(Either double click or right click->Document object->open)

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

1. Guided Questionnaire for pregnancy related adverse events
2. Guided Questionnaire for Medication Errors

Guided Questionnaire
Pregnancy-Related Adverse Events

AER:	
Site No:	
Patient ID/Initials:	
Patient Gender:	❑ M ❑ F

Local Case ID:	
Patient Date of Birth (dd-MMM-yyyy):	
Other Patient Identifiers	

Oligohydramnios, some associated with fatal pulmonary hypoplasia, and fetal renal impairment have been observed in some patients treated with Herceptin in the post-marketing setting. Oligohydramnios has been identified as an important identified risk for Herceptin, while for Perjeta and Kadcyla, oligohydramnios has been classified as an important potential risk.

By filling out this questionnaire, you will help us to understand more fully the risk factors for this condition and associated abnormalities, to communicate potential adverse pregnancy complications and fetal/infant outcomes to Health Authorities, Healthcare Professionals and patients.

Reporter Information	
Name of reporter completing this form ***(if other than addressee, please provide contact information below)***:	
Health Care Provider? ❑ Yes ❑ No - Please Specify:	
Phone number:	Fax number:
Email address:	

☐ Drug: **Herceptin** Lot Number(s):_____
☐ Drug: **Perjeta** Lot Number(s):_____
☐ Drug: **Kadcyla** Lot Number(s):_____

Maternal Information

	Selected Medical History		Comment
☐	None	☐ Unknown	
☐	Hypertension		
☐	Diabetes; if yes, specify type		
☐	Seizure disorders		
☐	Thyroid disorder		
☐	Smoking / use of alcohol; specify		
☐	Family history of diabetes mellitus		
☐	Family history of congenital renal anomalies; if yes, specify		
☐	Other; specify		

	Selected Obstetric History (*previous pregnancies*)		Please, provide specifics including contributing factors
☐	None	☐ Unknown	
☐	Gestational hypertension/preeclampsia/eclampsia		
☐	Gestational diabetes		
☐	Spontaneous or induced abortions; if yes/known, specify cause		

☐	Oligohydramnios		
☐	History of other pregnancy complications; specify		
☐	Other; specify		
	Fetal Abnormalities in Previous Pregnancies		Please, provide specifics including contributing factors
☐	None	☐ Unknown	
☐	Delayed renal development		
☐	Death in utero; if yes/known, specify reason		
☐	Birth defects; if yes, specify		
☐	Family history of birth defects; if yes, specify		
☐	Other; specify		

Current Pregnancy

Pre-pregnancy weight and height	Weight:	Height:
Blood pressure prior to conception	Date:	BP:

Prenatal Imaging and Aneuploidy Screening/testing (e.g., ultrasound, amniocentesis, etc.)

Was a prenatal test performed? ☐ Yes ☐ No

If yes, Prenatal Test Type	Date	Indication for test	Was a defect noted?	Specify

Ultrasound Assessment Log

Date	Gestational Age	Amniotic Fluid (AF) Measurement	Provider's Assessment of AF	Estimated Fetal Weight	Reported Percentile Growth	Provider's Assessment of Growth
	_____ weeks	AF Index _____ cm Maximum Vertical Pocket _____ cm Other _____ □ AF not measured	1 Normal 2 Abnormal 3 Oligohydramnios 4 Anhydramnios 5 Polyhydramnios 6 Delayed renal development 7 Other: _____ 8 Not assessed	_____ grams ☐ Not estimated	_____ ☐ Not reported ☐ Growth not measured	☐ Normal ☐ Abnormal ☐ IUGR* (< 10%ile) ☐ Severe IUGR (< 3%ile) ☐ Large for Gestational Age (> 90%ile) ☐ Growth not measured

* IUGR=Intrauterine growth retardation

Concomitant Medications, including ACE inhibitors and prostaglandin synthase inhibitors and all known teratogens up to 6 months prior to conception or during pregnancy:				
Product Name	**Indication**	**Total daily dose**	**Start date**	**Stop date/Ongoing**

	Maternal Medical Conditions During Current Pregnancy *Please check all that apply and provide detailed information on pregnancy-related complications on last page*			
☐	Gestational Hypertension/ Preeclampsia/Eclampsia ☐ chronic hypertension ☐ pregnancy-induced hypertension ☐ Preeclampsia-eclampsia ☐ Preeclampsia superimposed on chronic hypertension	Diagnostic tests:	Start date / Gestational age	Contributing factors
☐	Gestational Diabetes	Diagnostic tests:	Start date / Gestational age	Contributing factors
☐	Spontaneous or induced abortions; if yes/known, specify cause	Pathology results:	Start date / Gestational age	Contributing factors
☐	Chronic leakage of amniotic fluid	Start date / Gestational age		Contributing factors
☐	Other; specify	Pathology results:	Start date / Gestational age	Contributing factors
	Fetal Conditions During Current Pregnancy *Please check all that apply and provide detailed information on fetal complications on last page*			
☐	Renal abnormalities in fetus ☐ Normal fetal kidneys and fluid filled bladder ☐ Delayed renal development ☐ Renal agenesis ☐ Cystic dysplasia ☐ Ureteral obstruction	Diagnostic tests: ☐ Ultrasonography	Start date / Gestational age	Contributing factors
☐	Fetal abnormalities, including genetic disorders; if yes, specify	Diagnostic tests: ☐ Ultrasound ☐ Alpha-fetoprotein ☐ Amniocentesis ☐ Aneuploidy screening ☐ Other	Date / Gest. age	Specify
☐	Post-maturity syndrome	Evidence:	Start date / Gestational age	Contributing factors
☐	Death in utero; if yes/known, specify reason	Pathology results:	Date / Gestational age	Contributing factors
☐	Other; specify			

Infant information

Mode of birth	☐ Spontaneous vaginal delivery ☐ Forceps / vacuum ☐ Cesarean section	Date	
Gestational age at birth		Apgar score	

Please check all that apply and provide detailed information on complications in infants on last page

	Date of Assessment			Contributing factors
☐	Birth outcome	☐ Live birth ☐ Neonatal death	Cause	
☐	Small for gestational age at birth (SGA)	☐ Gestational age ☐ Weight/length	Date of assessment	
☐	Congenital anomalies	☐ Major malformation A defect that has either cosmetic or functional significance to the child	Specify	
		☐ Minor malformation A defect that occurs infrequently but has neither cosmetic nor functional significance to the child	Specify	
		☐ Deformation A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)	Specify	
		☐ Disruption A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin)	Specify	
☐	Abnormal renal function	☐ Proteinuria ☐ Electrolyte imbalance ☐ Other	Lab results	
☐	Other; specify			

FOR INTERNAL USE ONLY
Company Awareness Date:
MCN:

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: .....

Contact name for further information on pregnancy and/or on the infant:

.....

Function ..... Tel. No.: .....

Contact Address: ..... Fax No.: .....

..... Email: .....

.....

Detailed information on pregnancy-related complications

Please enter text in dynamic box below:

Roche

Herceptin Guided Questionnaire
Medication Errors

Patient ID/Initials:	
Patient Gender:	❑ M ❑ F
Patient Date of Birth (dd-MMM-yyyy):	
Patient Weight	Kg Lb

AER:	
Site No:	
Local Case ID:	

With the introduction of the new Herceptin subcutaneous (SC) formulation, medication errors may occur.

By filling in this questionnaire, you will help us to gain an understanding of the types of errors that occur which would enable preventative measures to be put into place.

Reporter Information	
Name of reporter completing this form **(if other than addressee, provide contact information below):**	
Health Care Provider? ❑ Yes ❑ No-Specify:	
Phone number:	Fax number:
Email address:	

Details of medication error:	
Date of medication error (dd-mmm-yyyy):	Herceptin Start Date (dd-mmm-yyyy):
Herceptin Indication:	Dosage administered:
Formulation Administered: ❑ Herceptin IV ❑ Herceptin SC	Route of Administration: ❑ Intravenous (IV) ❑ Subcutaneous (SC)
Description of the error (e.g. incorrect route, incorrect dose or overdose, accidental exposure, wrong technique in drug usage process, drug administration error etc)	

Herceptin (trastuzumab) Treatment Details		
Please provide details of the <u>prescribed or intended</u> treatment details for Herceptin		
Herceptin Indication:		
Start Date:	End Date (if applicable):	
Treatment dosage:		❑ 3-weekly ❑ weekly
Formulation prescribed: ❑ Herceptin IV ❑ Herceptin SC		

Adverse Events (as a result of the medication error)		
Adverse Event	**Onset Date (dd-mmm-yyyy)**	**Event Outcome (date if applicable: dd-mmm-yyyy)**
1.		
2.		
3.		
4.		

Relevant Medical History and Clinical Conditions

Concurrent/Previous Anti-neoplastic Drug Information			
Drug name Generic/Trade	Start Date	Stop Date	On going
			❑ Yes
			❑ Yes
			❑ Yes

Other Concomitant Medications			
Drug name Generic/Trade	Start Date	Stop Date	On going
			❑ Yes
			❑ Yes
			❑ Yes

Relevant Laboratory Tests/Diagnostic Data						
Test	Baseline (pre-event onset)		At Event Onset		Following Event Resolution	
	Date	Results	Date	Results	Date	Results

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

ANNEX 5

PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

NOT APPLICABLE

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (if applicable)

NOT APPLICABLE

ANNEX 7:

OTHER SUPPORTING DATA

(INCLUDING REFERENCED MATERIAL)

ANNEX 7: OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

LIST OF PTS FOR IMPORTANT IDENTIFIED RISKS

CARDIAC DYSFUNCTION

Cardiac Failure (SMQ)-Wide

Acute left ventricular failure
Acute pulmonary oedema
Acute right ventricular failure
Artificial heart implant
Atrial natriuretic peptide abnormal
Atrial natriuretic peptide increased
Bendopnoea
Brain natriuretic peptide abnormal
Brain natriuretic peptide increased
Cardiac asthma
Cardiac cirrhosis
Cardiac contractility modulation therapy
Cardiac dysfunction
Cardiac failure
Cardiac failure acute
Cardiac failure chronic
Cardiac failure congestive
Cardiac failure high output

Cardiac index decreased
Cardiac output decreased
Cardiac resynchronisation therapy
Cardiac ventriculogram abnormal
Cardiac ventriculogram left abnormal
Cardiac ventriculogram right abnormal
Cardio-respiratory distress
Cardiogenic shock
Cardiomegaly
Cardiopulmonary failure
Cardiorenal syndrome
Cardiothoracic ratio increased
Central venous pressure increased
Chronic left ventricular failure
Chronic right ventricular failure
Cor pulmonale
Cor pulmonale acute
Cor pulmonale chronic
Diastolic dysfunction
Dilatation ventricular
Dyspnoea paroxysmal nocturnal
Ejection fraction decreased
Heart transplant
Hepatic congestion
Hepatic vein dilatation

Hepatojugular reflux

Intracardiac pressure increased

Jugular vein distension

Left ventricular diastolic collapse

Left ventricular dilatation

Left ventricular dysfunction

Left ventricular enlargement

Left ventricular failure

Low cardiac output syndrome

Lower respiratory tract congestion

Myocardial depression

N-terminal prohormone brain natriuretic peptide abnormal

N-terminal prohormone brain natriuretic peptide increased

Neonatal cardiac failure

Nocturnal dyspnoea

Obstructive shock

Oedema

Oedema blister

Oedema due to cardiac disease

Oedema neonatal

Oedema peripheral

Orthopnoea

Peripheral oedema neonatal

Peripheral swelling
Post cardiac arrest syndrome
Prohormone brain natriuretic peptide abnormal
Prohormone brain natriuretic peptide increased
Pulmonary congestion
Pulmonary oedema
Pulmonary oedema neonatal
Radiation associated cardiac failure
Right ventricular diastolic collapse
Right ventricular dilatation
Right ventricular dysfunction
Right ventricular ejection fraction decreased
Right ventricular enlargement
Right ventricular failure
Scan myocardial perfusion abnormal
Stroke volume decreased
Surgical ventricular restoration
Systolic dysfunction
Venous pressure increased
Venous pressure jugular abnormal
Venous pressure jugular increased
Ventricular assist device insertion
Ventricular compliance decreased
Ventricular dysfunction
Ventricular dyssynchrony

Ventricular failure

Wall motion score index abnormal

ADMINISTRATION-RELATED REACTIONS

MedDRA terms: ‘Modified Anaphylactic Reaction basket’ which consists of the Anaphylactic Reaction SMQ plus the individual PTs:

Infusion-Related Reaction; and Injection Site Hypersensitivity, Hypersensitivity and drug hypersensitivity.

Herceptin-Specific AEGT-Anaphylaxis+IRR

Acquired C1 inhibitor deficiency
Acute respiratory failure
Allergic oedema
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Angioedema
Asthma
Blood pressure decreased
Blood pressure diastolic decreased
Blood pressure systolic decreased
Bronchial oedema
Bronchospasm
Cardiac arrest
Cardio-respiratory arrest
Cardio-respiratory distress

Cardiovascular insufficiency
Chest discomfort
Choking
Choking sensation
Circulatory collapse
Circumoral oedema
Cough
Cyanosis
Dialysis membrane reaction
Diastolic hypotension
Dyspnoea
Erythema
Eye oedema
Eye pruritus
Eye swelling
Eyelid oedema
Face oedema
Fixed eruption
Flushing
Generalised erythema
Hereditary angioedema with C1 esterase inhibitor deficiency
Hyperventilation
Hypotension
Injection site urticaria
Irregular breathing

Kounis syndrome
Laryngeal dyspnoea
Laryngeal oedema
Laryngospasm
Laryngotracheal oedema
Lip oedema
Lip swelling
Mouth swelling
Nasal obstruction
Nodular rash
Ocular hyperaemia
Oedema
Oedema blister
Oedema mouth
Oropharyngeal oedema
Oropharyngeal spasm
Oropharyngeal swelling
Periorbital oedema
Pharyngeal oedema
Procedural shock
Pruritus
Pruritus allergic
Pruritus generalised
Rash
Rash erythematous

Rash generalised
Rash pruritic
Respiratory arrest
Respiratory distress
Respiratory dyskinesia
Respiratory failure
Reversible airways obstruction
Sensation of foreign body
Shock
Shock symptom
Skin swelling
Sneezing
Stridor
Swelling
Swelling face
Swollen tongue
Tachypnoea
Throat tightness
Tongue oedema
Tracheal obstruction
Tracheal oedema
Type I hypersensitivity
Upper airway obstruction
Urticaria
Urticaria papular

Wheezing

Hypersensitivity

Drug hypersensitivity

Infusion Related Reaction

Injection Site hypersensitivity

OLIGOHYDRAMNIOS

MedDRA Terms: MedDRA High Level Group Term (HLGT): Neonatal and perinatal conditions; and, MedDRA HLT: Amniotic fluid and cavity disorders of pregnancy NEC and following PTs: Amniotic fluid index, Amniotic fluid index abnormal, Amniotic fluid index decreased, Amniotic fluid index increased, Amniotic fluid volume, Amniotic fluid volume decreased, Amniotic fluid volume increased, Intra-amniotic injection, Vesicoamniotic shunt.

HLGT - Neonatal and perinatal conditions

Abnormal organ growth
Abnormal organ maturation
ABO haemolytic disease of newborn
ABO incompatibility
Adrenal insufficiency neonatal
Adrenocortical insufficiency neonatal
Agitation neonatal
Alloimmunisation
Alveolar capillary dysplasia
Anaemia neonatal
Anaesthetic complication neonatal
Apparent life threatening event
Arrhythmia neonatal
Asymmetric gluteal fold
Atelectasis neonatal
Atrioventricular node dispersion
Benign familial neonatal convulsions

Birth trauma
Blood incompatibility haemolytic anaemia of newborn
Blood loss anaemia neonatal
Blood type incompatibility
Bradycardia neonatal
Breast milk substitute intolerance
Bronchopulmonary dysplasia
Caput succedaneum
Cardiac arrest neonatal
Cardiomyopathy neonatal
Cardio-respiratory arrest neonatal
Central nervous system lymphoma
Cephalhaematoma
Cerebral haemorrhage neonatal
Cerebral palsy
Circulatory failure neonatal
Coagulation disorder neonatal
Collodion baby
Coma neonatal
Congenital chylothorax
Congenital condyloma
Congenital cytomegalovirus infection
Congenital floppy infant
Congenital hepatitis B infection
Congenital herpes simplex infection

Congenital HIV infection
Congenital infection
Congenital malaria
Congenital pneumonia
Congenital pulmonary hypertension
Congenital rubella infection
Congenital syphilis
Congenital syphilitic encephalitis
Congenital syphilitic meningitis
Congenital toxoplasmosis
Congenital tuberculosis
Congenital varicella infection
Congenital Zika syndrome
Conjunctivitis gonococcal neonatal
Convulsion neonatal
Coxsackie viral disease of the newborn
Cranial nerve injury secondary to birth trauma
Cranial sutures widening
Craniotabes
Cronobacter necrotising enterocolitis
Cutaneous extramedullary haemopoiesis
Cyanosis neonatal
Death neonatal
Delayed visual maturation
Diarrhoea infectious neonatal

Diarrhoea neonatal
Disseminated intravascular coagulation in newborn
Disturbance of thermoregulation of newborn
Drug withdrawal syndrome neonatal
Dry lung syndrome
Ductus arteriosus premature closure
Ductus venosus agenesis
Dyskinesia neonatal
Encephalopathy neonatal
Erythema toxicum neonatorum
Erythroblastosis foetalis
Facial nerve injury due to birth trauma
Failure to thrive
Feeding intolerance
Fever neonatal
Fixed bowel loop
Floppy infant
Fontanelle bulging
Fontanelle depressed
Fracture of clavicle due to birth trauma
Funisitis
Gangrene neonatal
Gasping syndrome
Granulocytopenia neonatal
Grey syndrome neonatal

Group B streptococcus neonatal sepsis
Haemolysis neonatal
Haemorrhage neonatal
Haemorrhagic disease of newborn
Harlequin foetus
Harlequin skin reaction
Hepatitis neonatal
Hepatocellular damage neonatal
Hepatosplenomegaly neonatal
Herpes simplex virus conjunctivitis neonatal
Hyperbilirubinaemia neonatal
Hyperglycinaemia
Hyperkinesia neonatal
Hypertension neonatal
Hypertonia neonatal
Hypoglycaemia neonatal
Hypokinesia neonatal
Hypothermia neonatal
Hypotonia neonatal
Hypoventilation neonatal
Immature larynx
Immature respiratory system
Inclusion conjunctivitis neonatal
Infantile apnoea
Infantile back arching

Infantile colic
Infantile spitting up
Infantile vomiting
Injury to brachial plexus due to birth trauma
Injury to spinal cord secondary to birth trauma
Intoxication by breast feeding
Intraventricular haemorrhage neonatal
Isoimmune haemolytic disease
Jaundice neonatal
Junctional ectopic tachycardia
Kernicterus
Large for dates baby
Late metabolic acidosis of newborn
Lenticulostriatal vasculopathy
Leukopenia neonatal
Low birth weight baby
Lymphocytopenia neonatal
Meconium abnormal
Meconium aspiration syndrome
Meconium cyst
Meconium ileus
Meconium increased
Meconium peritonitis
Meconium plug syndrome
Melaena neonatal

Meningitis neonatal
Meningoencephalitis herpes simplex neonatal
Myasthenia gravis neonatal
Necrotising enterocolitis neonatal
Neonatal alloimmune thrombocytopenia
Neonatal alveolar aeration excessive
Neonatal anoxia
Neonatal anuria
Neonatal asphyxia
Neonatal aspiration
Neonatal behavioural syndrome
Neonatal candida infection
Neonatal cardiac failure
Neonatal cholestasis
Neonatal complications of substance abuse
Neonatal deafness
Neonatal diabetes mellitus
Neonatal disorder
Neonatal gastrointestinal disorder
Neonatal gastrointestinal haemorrhage
Neonatal haemochromatosis
Neonatal hepatomegaly
Neonatal hypoacusis
Neonatal hypocalcaemia
Neonatal hyponatraemia

Neonatal hypoparathyroidism
Neonatal hypotension
Neonatal hypoxia
Neonatal infection
Neonatal infective mastitis
Neonatal insufficient breast milk syndrome
Neonatal intestinal dilatation
Neonatal intestinal obstruction
Neonatal intestinal perforation
Neonatal leukaemia
Neonatal lupus erythematosus
Neonatal mucocutaneous herpes simplex
Neonatal multi-organ failure
Neonatal oversedation
Neonatal pneumonia
Neonatal respiratory acidosis
Neonatal respiratory alkalosis
Neonatal respiratory arrest
Neonatal respiratory depression
Neonatal respiratory distress
Neonatal respiratory distress syndrome
Neonatal respiratory failure
Neonatal tachycardia
Neonatal tachypnoea
Neonatal testicular torsion

Neonatal tetany
Neonatal thyrotoxicosis
Neonatal toxicity
Netherton's syndrome
Neuroendocrine cell hyperplasia of infancy
Neutropenia neonatal
Newborn head moulding
Oedema neonatal
Omphalitis
Omphalorrhexis
Ophthalmia neonatorum
Overfeeding of infant
Perinatal brain damage
Perinatal HBV infection
Perinatal HIV infection
Perinatal stroke
Peripheral oedema neonatal
Periventricular haemorrhage neonatal
Periventricular leukomalacia
Persistent foetal circulation
Polycythaemia neonatorum
Poor feeding infant
Poor sucking reflex
Poor weight gain neonatal
Posthaemorrhagic hydrocephalus

Postmature baby
Premature baby
Premature baby death
Primary familial hypomagnesaemia
Pulmonary air leakage
Pulmonary dysmaturity syndrome
Pulmonary lymphangiectasia
Pulmonary oedema neonatal
Purpura neonatal
Rash neonatal
Renal failure neonatal
Renal impairment neonatal
Respiratory disorder neonatal
Respiratory tract haemorrhage neonatal
Retinopathy of prematurity
Rhesus haemolytic disease of newborn
Rhesus incompatibility
Sepsis neonatal
Single umbilical artery
Small for dates baby
Somnolence neonatal
Subarachnoid haemorrhage neonatal
Subdural haemorrhage neonatal
Subgaleal haematoma
Subgaleal haemorrhage

Sudden infant death syndrome
Term baby
Tetanus neonatorum
Thrombocytopenia neonatal
Thrombophlebitis neonatal
Transient hypogammaglobulinaemia of infancy
Transient hypothyroxinaemia of prematurity
Transient neonatal pustular melanosis
Transient tachypnoea of the newborn
Tremor neonatal
Umbilical artery hypoplasia
Umbilical cord abnormality
Umbilical cord around neck
Umbilical cord compression
Umbilical cord cyst
Umbilical cord haemorrhage
Umbilical cord occlusion
Umbilical cord prolapse
Umbilical cord short
Umbilical cord thrombosis
Umbilical cord vascular disorder
Umbilical discharge
Umbilical granuloma
Umbilical malformation
Umbilical sepsis

Urinary tract infection neonatal
Venous thrombosis neonatal
Virilism foetal
Vision abnormal neonatal
Weight decrease neonatal
Zika virus associated birth defect
Zika virus associated ocular birth defect

HLT - Amniotic fluid and cavity disorders of pregnancy NEC

Amniorrhexis
Amniorrhoea
Amniotic band syndrome
Amniotic cavity disorder
Amniotic cavity infection
Amniotic infection syndrome of Blane
Meconium in amniotic fluid
Meconium stain
Oligohydramnios
Polyhydramnios

1. CARDIAC DYSFUNCTION

1.1 FREQUENCY WITH 95% CI:

Table 1 Cardiac Dysfunction, Severity and Frequency – M77001

Treatment: Docetaxel Alone1; N=94					
CTC Grade	**1**	**2**	**3**	**4**	**5**
Cardiotoxicity *	18 (19.1%)	15 (16.0%)	4 (4.3%)	0 (0.0%)	0 (0.0%)
Oedema	2 (2.1%)	0 (0.0%)	2 (2.1%)	0 (0.0%)	0 (0.0%)
Oedema Peripheral	16 (17.0%)	15 (16.0%)	2 (2.1%)	0 (0.0%)	0 (0.0%)
Treatment: Docetaxel plus Trastuzumab; N=92					
CTC Grade	**1**	**2**	**3**	**4**	**5**
Cardiotoxicity *	24 (26.1%)	17 (18.5%)	2 (2.2%)	0 (0.0%)	0 (0.0%)
Ejection Fraction Decreased	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Left Ventricular Failure	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oedema	4 (4.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oedema Peripheral	21 (22.8%)	15 (16.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Pitting Oedema	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1] There were 41 patients originally randomised in docetaxel alone and who switched during the study and received trastuzumab. AEs for these patients were not recorded, therefore the summary is not provided.

* Number of highest CTC grade per patient, estimated on the subset of patients with at least one Cardiac dysfunction related term.

Percentages are based on the total number of patients in treatment group.

Table 2 Cardiac Dysfunction, Severity & Frequency: BO16216

[1]Anastrozole alone; N=104					
CTC Grade	1	2	3	4	5
Cardiotoxicity*	0 (0.0%)	0 (0.0%)	2 (1.9%)	0 (0.0%)	0 (0.0%)
Oedema Peripheral	0 (0.0%)	0 (0.0%)	2 (1.9%)	0 (0.0%)	0 (0.0%)
Anastrozole + Trastuzumab; N=103					
CTC Grade	1	2	3	4	5
Cardiotoxicity*	6 (5.8%)	5 (4.9%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Cardiac Failure	0 (0.0%)	2 (1.9%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Oedema	2 (1.9%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oedema Peripheral	5 (4.9%)	2 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
[2]Anastrozole alone after start of Trastuzumab; N=58					
CTC Grade	1	2	3	4	5
Cardiotoxicity*	3 (5.2%)	5 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac Failure	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ejection Fraction Decreased	2 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oedema	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oedema Peripheral	1 (1.7%)	3 (5.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

(1) For patients originally randomized in anastrozole alone arm and who switched to trastuzumab, only AEs before the first trastuzumab administration are summarised.

(2) Cross-over patients: anastrozole + trastuzumab after having anastrozole alone until progression of disease.

(*) Number of highest CTC grade per patient, estimated on the subset of patients with at least one Cardiac dysfunction related term.

Note: Percentages are based on the total number of patients in treatment group.

Table 3 Cardiac Dysfunction, Severity: BO18255 (Gastric Cancer)

Cardiac Dysfunction , Severity
Safety Evaluable Patients

	Fluoropyrimidine/Cisplatin (n=290)				Trastuzumab/Fluoropyrimidine/Cisplatin (n=294)			
CTC GRADE	1	2	3	4	1	2	3	4
CARDIAC FAILURE	0	0	1	1	0	0	0	1
CARDIAC FAILURE CONGESTIVE	0	0	0	0	0	0	0	1
EJECTION FRACTION DECREASED	0	0	0	0	1	0	1	0
LEFT VENTRICULAR DYSFUNCTION	0	0	0	0	0	1	0	0
OEDEMA	22	4	0	0	22	3	0	0
OEDEMA PERIPHERAL	8	4	1	0	13	4	1	0

Table 4 Cardiac Dysfunction, Frequency: AEs by Patient-Years– BO18255 (Gastric Cancer)

Cardiac Dysfunction, Frequency: AEs by Patient-Years
Safety Evaluable Patients

	Fluoropyrimidine/Cisplatin (n=290)	Trastuzumab/Fluoropyrimidine/Cisplatin (n=294)
Total Patient Years	201.39	287.26
Oedema		
Number of Patients with an Event	26	25
Total Number of Events	28	28
Events per Patient Year	0.14	0.10
Events per 100 Patients Years	13.90	9.75
Oedema Peripheral		
Number of Patients with an Event	13	18
Total Number of Events	15	25
Events per Patient Year	0.07	0.09
Events per 100 Patients Years	7.45	8.70
Cardiac Failure		
Number of Patients with an Event	2	1
Total Number of Events	2	1
Events per Patient Year	0.01	0.00
Events per 100 Patients Years	0.99	0.35
Cardiac Failure Congestive		
Number of Patients with an Event		1
Total Number of Events		1
Events per Patient Year		0.00
Events per 100 Patients Years		0.35
Ejection Fraction Decreased		
Number of Patients with an Event		2
Total Number of Events		2
Events per Patient Year		0.01
Events per 100 Patients Years		0.70

Left Ventricular Dysfunction	
Number of Patients with an Event	1
Total Number of Events	1
Events per Patient Year	0.00
Events per 100 Patients Years	0.35

Table 5 Cardiac Dysfunction, Severity & Frequency: BO22227 IV ARM

stae17cf_se Summary of CTC Grading (Worst Case) for Cardiac Failure - SMQ Broad (SMQ) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB IV; N = 298

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	56	(19)	43	(14)	16	(5)	-		-		-	
Total Number of AEs	63		47		16		-		-		-	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS												
Total Pts With at Least one AE	43	(14)	37	(12)	7	(2)	-		-		-	
OEDEMA PERIPHERAL	30	(10)	27	(9)	3	(1)	-		-		-	
OEDEMA	15	(5)	12	(4)	3	(1)	-		-		-	
PERIPHERAL SWELLING	3	(1)	2	(<1)	1	(<1)	-		-		-	
Total Number of AEs	48		41		7		-		-		-	
CARDIAC DISORDERS												
Total Pts With at Least one AE	13	(4)	5	(2)	8	(3)	-		-		-	
LEFT VENTRICULAR DYSFUNCTION	12	(4)	4	(1)	8	(3)	-		-		-	
CARDIAC FAILURE	1	(<1)	1	(<1)	-		-		-		-	
Total Number of AEs	13		5		8		-		-		-	
INVESTIGATIONS												
Total Pts With at Least one AE	1	(<1)	-		1	(<1)	-		-		-	
EJECTION FRACTION DECREASED	1	(<1)	-		1	(<1)	-		-		-	
Total Number of AEs	1		-		1		-		-		-	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS												
Total Pts With at Least one AE	1	(<1)	1	(<1)	-		-		-		-	
NOCTURNAL DYSPNOEA	1	(<1)	1	(<1)	-		-		-		-	
Total Number of AEs	1		1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
AE17 03MAY2017:22:22:16 (1 of 2)

Table 6 Cardiac Dysfunction, Severity & Frequency: BO22227 SC ARM

stae17cf_se Summary of CTC Grading (Worst Case) for Cardiac Failure - SMQ Broad (SMQ) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB SC; N = 297

Body System/ Adverse Event	Total		CTC Grading 1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	47	(16)	38	(13)	7	(2)	3	(1)	-		-	
Total Number of AEs	52		41		7		4		-		-	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS												
Total Pts With at Least one AE	33	(11)	31	(10)	2	(<1)	-		-		-	
OEDEMA PERIPHERAL	23	(8)	22	(7)	1	(<1)	-		-		-	
OEDEMA	10	(3)	9	(3)	1	(<1)	-		-		-	
PERIPHERAL SWELLING	3	(1)	3	(1)	-		-		-		-	
Total Number of AEs	36		34		2		-		-		-	
CARDIAC DISORDERS												
Total Pts With at Least one AE	15	(5)	7	(2)	5	(2)	3	(1)	-		-	
LEFT VENTRICULAR DYSFUNCTION	10	(3)	4	(1)	5	(2)	1	(<1)	-		-	
CARDIAC FAILURE CONGESTIVE	2	(<1)	-		-		2	(<1)	-		-	
CARDIAC FAILURE	1	(<1)	-		-		1	(<1)	-		-	
DIASTOLIC DYSFUNCTION	1	(<1)	1	(<1)	-		-		-		-	
LEFT VENTRICULAR DILATATION	1	(<1)	1	(<1)	-		-		-		-	
RIGHT VENTRICULAR FAILURE	1	(<1)	1	(<1)	-		-		-		-	
Total Number of AEs	16		7		5		4		-		-	

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
AE17 03MAY2017:22:22:16 (2 of 2)

1.2 SERIOUSNESS/ OUTCOMES:

Clinical Studies: Metastatic Breast Cancer:

- **M77001**

The action taken with study medications docetaxel and trastuzumab in response to each AE in both study arms were as follows: docetaxel alone arm (total AEs 53); none taken (43), dosage modified (2) and discontinued (8); docetaxel plus trastuzumab arm (total AEs 63); none taken (57), dosage modified (2) and discontinued (4). The dose of docetaxel used in this study was 100 mg/m^2 IV on study Day 2; followed by docetaxel 100 mg/m^2 IV every 3 weeks.

Across the two treatment arms, cardiac AEs were mainly mild to moderate in severity: docetaxel alone arm – mild 18, moderate 15, and severe 4; docetaxel plus trastuzumab arm – mild 24, moderate 18, and severe 2 (NB; individual patients may have experienced the same cardiac AE on more than one occasion and captured here is the worst case intensity occurrence, therefore the number of AEs assigned severity values does not necessarily match the total number of AEs).

Outcomes at AE level by treatment arm

Overall, in each of the treatment arms, the percentage of outcomes expressed as a total of the number of AEs were as follows: docetaxel alone arm (total AEs 53) – resolved 36, persisting 16, and fatal 1; docetaxel plus trastuzumab arm (total AEs 63) – resolved 51, resolved with sequelae 1, and persisting 11.

- **BO16216**

The action taken with study medications anastrozole and trastuzumab in response to each AE in all three study arms were as follows: anastrozole alone arm (total AEs 4) – none taken; anastrozole plus trastuzumab arm (total AEs 16) – none taken (11), dosage modified (3) and discontinued (2); anastrozole alone after start of trastuzumab arm (total AEs 10) – none taken (4), dosage modified (2) and discontinued (4). No cardiac deaths were reported.

Outcomes at AE level by treatment arm

Overall, in each of the treatment arms, the outcomes at AE level were as follows: anastrozole alone arm (total AEs 4) – resolved 2 and persisting 2; anastrozole plus trastuzumab arm (total AEs 16) – resolved 11 and persisting 5; anastrozole alone after start of trastuzumab arm (total AEs 10) – resolved 3 and persisting 7.

Early Breast Cancer (EBC)

Adjuvant Treatment in EBC

- **BCIRG-006 (H2296s)/GO00773)**

Please refer to Table 7 which summarizes symptomatic cardiac events reported at any time during the study. The most frequently occurring symptomatic cardiac event was Grade 3/4 CLVF (cardiac left ventricular function) which corresponds to symptomatic CHF. The incidence was highest in the AC→TH arm (1.9%) and increased relative to both AC→T (0.3%) and TCH arms (0.4%). The overall incidence was highest in the AC→TH arm largely due to the incidence of Grade 3/4 CLVF. Please refer to Table 7 to Table 10 in for further information.

Table 7 Symptomatic Cardiac Events per Independent Cardiac Review Panel (ICRP) Occurring at Any Time during the Study: Safety Population - BCIRG 006 (H2296s/GO00773)

Event Type	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
CHF (Grade 3/4 CLVF)	3 (0.3%)	20 (1.9%)	4 (0.4%)
Grade 3/4 cardiac ischemia/infarction	0 (0.0%)	2 (0.2%)	2 (0.2%)
Grade 3/4 arrhythmia	3 (0.3%)	2 (0.2%)	6 (0.6%)
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any symptomatic cardiac event [a]	6 (0.6%)	23 (2.2%)	12 (1.1%)

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; CHF=congestive heart failure; CLVF=cardiac left ventricular function; SD=standard deviation; TCH=docetaxel, carboplatin, and Herceptin.

[a] A patient could be included in more than one event type category; therefore, the "any symptomatic cardiac event row" is less the sum of number of events in a given column.

Asymptomatic LVEF Declines

Per the protocol, seven left ventricular ejection fraction (LVEF) evaluations were to be performed during treatment and follow-up. Overall, compliance with the protocol-specified LVEF assessment schedule was high for patients in all three arms (AC→T: 80.6%, AC→TH: 84.7%, and TCH: 83.6%).

Table 8 Asymptomatic and Symptomatic LVEF Declines by Baseline Events BCIRG 006 (H2296s/GO00773)

Event Type	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Absolute decline of > 15% from baseline and to a value below the LLN	43 (4.1%)	109 (10.2%)	36 (3.4%)
Absolute decline of > 10% from baseline and to a value below 50%	60 (5.7%)	130 (12.2%)	48 (4.5%)
Symptomatic and/or asymptomatic decline of > 15%, below the LLN	45 (4.3%)	115 (10.8%)	47 (4.5%)

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; ANC=absolute neutrophil count; LLN=lower limit of normal; TCH=docetaxel, carboplatin, and Herceptin.

Timing of Symptomatic Cardiac and LVEF Events

The timing of symptomatic cardiac and LVEF events is presented in Table 9. The majority of all events occurred during trastuzumab monotherapy or follow-up.

Table 9 Timing of First Symptomatic and LVEF Events: Safety Population BCIRG 006 (H2296s/GO00773)

Type and Timing of Event	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Symptomatic cardiac event			
All periods	6 (0.6%)	23 (2.2%)	12 (1.1%)
During AC	0 (0.0%)	0 (0.0%)	—
During T, TH, and TCH	1 (0.1%)	3 (0.3%)	4 (0.4%)
During Herceptin monotherapy or follow-up	5 (0.5%)	20 (1.9%)	8 (0.8%)
Absolute decline of > 15% in LVEF from baseline and to a value below the LLN			
All periods	43 (4.1%)	109 (10.2%)	36 (3.4%)
During AC	2 (0.2%)	5 (0.5%)	—
During T, TH, and TCH	12 (1.1%)	27 (2.5%)	14 (1.3%)
During Herceptin monotherapy or follow-up	29 (4.1%)	77 (7.2%)	22 (2.1%)
Symptomatic and/or LVEF event			
All periods	45 (4.3%)	115 (10.8%)	47 (4.5%)
During AC	2 (0.2%)	5 (0.5%)	—
During T, TH, and TCH	12 (1.1%)	29 (2.7%)	18 (1.7%)
During Herceptin monotherapy or follow-up	31 (3.0%)	81 (7.6%)	29 (2.7%)

A=doxorubicin; AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; C=cyclophosphamide in AC arms and carboplatin or cisplatin in TCH arm; LLN=lower limit of normal; LVEF=left ventricular ejection fraction; T=docetaxel; TCH=docetaxel, carboplatin, and Herceptin; TH=docetaxel and Herceptin.

At 3 years, the rate of symptomatic cardiac events was 0.5%, 2.4%, and 1.16% in the AC→T, AC→TH, and TCH arms, respectively. For symptomatic CHF (Grade 3/4 CLVF), the 3-year rate was 0.3%, 2.1%, and 0.4% in the AC→T, AC→TH, and TCH arms, respectively.

An overall summary of cardiac adverse events is presented in Table 10 (Annex 7). The overall incidence of cardiac AEs was increased by 10.6% in the AC→TH arm relative to the AC→T arm. The overall incidence of cardiac AEs was increased by 7.5% in the TCH arm relative to the AC→T arm. The overall incidence of cardiac AEs was slightly higher in the AC→TH arm relative to the TCH arm; however, the incidence of serious and Grade 3/4 cardiac AEs is similar for the two arms. Cardiac AEs resulting in study treatment discontinuation or hospitalization were infrequent. Approximately, 9% of patients in the AC→TH and TCH arms experienced cardiac AEs classified as possibly- or probably-related to trastuzumab.

The most frequently reported (in ≥4% of all patients) cardiac AEs included hypertension (18.6%), palpitations (8.3%), sinus tachycardia (4.7%), and CLVF (4.0%). The overall incidence of CLVF AEs was increased by ≥2% in the AC→TH arm relative to both the AC→T and TCH arms.

The overall incidence of hypertension was increased by more than 2% in both trastuzumab-containing arms compared with AC→T. Of note, the incidence of Grade 3 or 4 hypertension was highest in the TCH arm and was increased by ≥2% relative to the AC→T arm. No additional notable differences were present in the occurrence of cardiac AEs.

Table 10 Cardiac Adverse Events Occurring at Any Time during the Study: Safety Population BCIRG 006 (H2296s/GO00773)

Genentech Inc., F. Hoffmann-La Roche Ltd & Sanofi-Aventis Group
10-year follow-up Analysis Update

Phase III Study: BCIRG006 (H2996s, TAX_GMA_302)
Adjuvant Herceptin Therapy in Breast Cancer

Table 5.3/5
Overview of Cardiac Adverse Events Occurring at Any Time during the Study
Safety Population

Type of Cardiac Adverse Event	AC -> T (n=1018)	AC -> TH (n=1100)	TCH (n=1056)	All Patients (n=3174)
Any cardiac adverse events	373 (36.6%)	527 (47.9%)	471 (44.6%)	1371 (43.2%)
Grade 3-4	50 (4.9%)	90 (8.2%)	92 (8.7%)	232 (7.3%)
Characterized as serious	18 (1.8%)	49 (4.5%)	35 (3.3%)	102 (3.2%)
Deemed possibly or probably related to study drug	91 (8.9%)	162 (14.7%)	136 (12.9%)	389 (12.3%)
Related to chemotherapy	90 (8.8%)	138 (12.5%)	106 (10.0%)	334 (10.5%)
Related to Herceptin	2 (0.2%)	98 (8.9%)	96 (9.1%)	196 (6.2%)
Resulting in study drug discontinuation	4 (0.4%)	16 (1.5%)	17 (1.6%)	37 (1.2%)
Discontinuation of chemotherapy	4 (0.4%)	2 (0.2%)	8 (0.8%)	14 (0.4%)
Discontinuation of Herceptin	(0.0%)	16 (1.5%)	16 (1.5%)	32 (1.0%)
With hospitalization as a consequence	18 (1.8%)	48 (4.4%)	40 (3.8%)	106 (3.3%)
With death as a consequence	2 (0.2%)	2 (0.2%)	3 (0.3%)	7 (0.2%)

AC=doxorubicin and cyclophosphamide; T=docetaxel; TCH=docetaxel, platinum salt, and Herceptin; TH=docetaxel and Herceptin.

Source: Biostatistics [redacted] pgm(/immuno/her2/bcirg006/pmc10yr/programs/t_cae_overall) output (t_cae_overall_rel)
Database (Cutoff 30DEC2014) Datasets (Dataaf)

The most frequently reported (in ≥4% of all patients) cardiac AEs included hypertension (18.6%), palpitations (8.3%), sinus tachycardia (4.7%), and CLVF (4.0%). The overall incidence of CLVF AEs was increased by ≥2% in the AC→TH arm relative to both the AC→T and TCH arms.

The overall incidence of hypertension was increased by more than 2% in both trastuzumab-containing arms compared with AC→T. Of note, the incidence of Grade 3 or 4 hypertension was highest in the TCH arm and was increased by ≥2% relative to the AC→T arm. No additional notable differences were present in the occurrence of cardiac AEs.

- **BO16348 (HERA)**

Based on a 10-year median follow-up of HERA data, the SAE of Cardiac dysfunction was reported in 53 patients and were distributed amongst the three study arms as follows: Observation Only arm (n=1744): 4/1744 (0.2%) patients; Herceptin-1-year arm (n=1682): 23/1682 (1.4%) patients; Herceptin-2-year arm (n=1673): 26/1673 (1.6%) patients. The most prominent cardiac SAE was cardiac failure congestive reported in 19/1682 (1.1%) patients (17 being assessed as related to trial treatment) in the Herceptin-1-year arm and 24/1673 (1.4%) patients (21 being assessed as related to trial treatment) in the Herceptin 2-year arm.

The 10-year median follow-up data reports death due to cardiac failure congestive occurred as follows during the study arms: Observation Only arm: 1/1744 (0.1%) patients; Herceptin-1-year: 2/1682 (0.1%) patients; Herceptin-2-year arm: 4/1673 (0.2%) patients. Of these seven cardiac failure congestive related fatal outcomes, three occurred during the first year of the study, one occurred in the 2-year treatment arm during the second year of the study and three deaths (two in the 1-year Herceptin arm and one in the 2-year Herceptin arm) occurred after the third year of the study during follow-up phase.

Cardiac failure congestive and peripheral swelling were the serious cardiac AEs leading to dose interruption- in the trastuzumab-containing arms: Herceptin-1-year arm: 1/1682 (0.06%) patient for each of the two events.

Cardiac Failure congestive was the most common cardiac serious AE leading to drug discontinuation in the trastuzumab-containing arms: Herceptin-1-year arm: 14/1682 (0.8%) patients; Herceptin-2-year arm: 21/1673 (1.3%) patients.

- **MO28048 (SafeHER)**

As of 10 March 2015, a total of 20 SAEs in 19 patients were reported for cardiac dysfunction. The most frequently reported cardiac SAE was cardiac failure congestive in 12 patients. In 10 patients, the SAE of cardiac failure congestive lead to drug discontinuation. No fatal events were reported.

- **Joint Analysis of NSABP B-31 and N9831**

Serious adverse events were not collected or reported in these two clinical trials. Grades 3-5 were reported; however, National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 (which did not contain Grade 5 coding) was utilized. Fatal outcomes, not necessarily designated as Grade 5, were captured and reported. Additionally, NCI-CTC version 2.0 (instead of MedDRA) coding of adverse events was utilized in clinical trial data collection or analysis.

Cardiac deaths were experienced by 2 patients (0.1%) in the AC→T + H group, 1 patient (0.3%) in the AC→T→H group, and 5 patients (0.3%) in the AC→T group.

In the AC→T + H group of the joint safety population, left ventricular events (i.e., symptomatic CHF [non-death] or cardiac death) were reported for 64 patients (3.2%). Events were reported for 12 patients during Herceptin + paclitaxel treatment (Period 2), 13 patients during Herceptin monotherapy (Period 3), and 32 patients during follow-up (Period 4). Events that could not be classified into any time period, because of uncertainty in the dosing records, were reported for 7 patients.

In the AC→T→H group, cardiac left ventricular events were reported for 7 patients. Events were reported for 2/984 of these patients during Herceptin monotherapy (Period 3) and 4/1023 during follow-up (Period 4). For 1 patient, an event was reported that could not be classified into any time period, because of uncertainty in the dosing records.

In the AC→T group, cardiac left ventricular events were reported for 21 patients. Events were reported for 2/887 of these patients during AC chemotherapy (Period 1), 2/823 during paclitaxel treatment (Period 2), and 16/734 during follow-up (Period 4). For 1 patient, an event was reported that could not be classified into any time period, because of uncertainty in the dosing records.

The AEs were not assessed as leading to study treatment withdrawal and/or discontinuation on the AE case report form (CRF) for either B-31 or N9831. The AEs leading to dose adjustment and outcomes of AEs were also not collected.

Neoadjuvant-adjuvant Treatment in EBC

- **MO16432 (NOAH)**

In the neoadjuvant-adjuvant setting trastuzumab was administered concurrently with an anthracycline the incidence of symptomatic cardiac dysfunction was low in the HER2+TC arm (patients with HER2-positive disease randomized to treatment with trastuzumab plus chemotherapy). More trastuzumab-treated patients had a decline in LVEF during the neoadjuvant part of the study but these were mostly declines of <10% points compared to baseline. Only 4 patients in the HER2+TC group (vs. one in the HER2+C group [Patients with HER2-positive disease randomized to treatment with chemotherapy alone] and none in the HER2−C group) [Parallel control group of patients

with HER2-negative disease treated with chemotherapy alone]) had a decline in LVEF of ≥10% points to an LVEF of <50%. From these 4 patients in the HER2+TC group only in one did the LVEF decline to <45%. The incidence of cardiac AEs during neoadjuvant therapy was similar in the two HER2-positive arms. During the follow-up period from 30 March 2009 to 14 July 2012, one Grade 3 cardiac AE of atrial fibrillation was reported in the HER2−C arm.

- **BO22227 (HannaH)**

Herceptin IV (n=298)

A total of 63 events were reported in 56 patients in the cardiac dysfunction risk grouping (SMQ: Cardiac failure Broad). None of these events were reported as serious. The most frequently reported AEs were peripheral oedema (30); oedema (15); left ventricular dysfunction (12), peripheral swelling (3) and one case each of ejection fraction decreased, cardiac failure and nocturnal dyspnea. A total of 56of the 63 AEs resolved without sequelae, while 6 AEs were unresolved and 1 AE of left ventricular dysfunction was resolved with sequelae at the time of the AE reports.

Herceptin SC (n=297)

A total of 52 events in 47 patients were reported in the cardiac dysfunction risk grouping (SMQ: Cardiac failure Broad). A total of 2 AEs (2 events of cardiac failure congestive) were assessed as serious.

The most frequently reported PTs were the same with the SC as for the IV formulation but with fewer AEs in the SC arm: peripheral edema (23); oedema (10); left ventricular dysfunction (10), peripheral swelling (3) and 2 events of cardiac failure congestive, one event each reporting diastolic dysfunction, cardiac failure and right ventricular failure. A total of 47 of the 52 total AEs resolved without sequelae; 2 resolved with sequelae; and 3 were unresolved at the time of the AE reports. There were no reports of fatal outcome from a cardiac dysfunction-related AE for both formulations.

- **MO22982 (PrefHER)**

Results from crossover period SC-IV or IV-SC (N=483 overall)

Herceptin IV (4 cycles)

15 patients (out of 478 patients) reported 17 cardiac events..

The most frequently reported AEs were Left ventricular dysfunction (in 5/478 patients [1.05%]) and bradycardia (in 3/478 patients [0.63%]) and palpitations and ejection fraction abnormal (in 2/479 patients each [0.442%])

Herceptin SC (4 cycles)

12 patients (out of 479 patients) reported 15 cardiac events.

The most frequently reported AEs were palpitations (in 3/479 patients [0.63%[), ejection fraction decreased (in 3/479 patients [0.63%]) and left ventricular dysfunction and cardiac failure congestive (each reported in 2/479 patients each [0.42%]).

Results from Herceptin continuation period

Cohort 1

A total of 226 patients in Cohort 1 received 1239 Herceptin IV cycles during the IV continuation period and 43 patients received 98 cycles administered with the SC SID during the SID self-administration period.

IV continuation: Cardiac AEs were reported for 7/226 (3.1%) patients during IV continuation period, none of which were left ventricular systolic dysfunction or congestive heart failure events. None of the cardiac AEs were serious or Grade ⩾3 events, or led to withdrawal from treatment.

SID self-administration: No cardiac AEs were reported for SID self-administration for SC SID period.

Cohort 2

Patients in Cohort 2 (SC Vial) continued to receive Herceptin SC via handheld syringe to complete their remaining cycles after the crossover period. A total of 208 patients in Cohort 2 received 1152 cycles with SC Vial during the SC continuation period and 10 patients received 34 cycles with IV during the IV continuation period.

SC vial continuation: Cardiac AEs were reported for 8/208 (3.8%) patients during the continuation period. Four patients experienced left ventricular dysfunction and 3 patients cardiac failure congestive.

IV continuation: Cardiac AEs were reported for 1/10 (10.0%) patients (Grade 1 event) and no left ventricular systolic dysfunction events were reported during the IV continuation period.

Table 11 Cardiac Dysfunction Summary MO22982 (Crossover SC-IV / IV-SC, EBC)

Cohort 1 and 2

System Organ Class Preferred Term	SC Period (N=479) n	(%)	E	IV Period (N=478) n	(%)	E
Number of Cardiac Adverse Events	12	(2.5)	15	15	(3.1)	17
Cardiac Disorders	8	(1.7)	11	14	(2.9)	14
Left Ventricular Dysfunction	2	(0.4)	2	5	(1.0)	5
Palpitations	3	(0.6)	5	2	(0.4)	2
Cardiac Failure Congestive	2	(0.4)	2	0		
Bradycardia	1	(0.2)	1	3	(0.6)	3
Extrasystoles	1	(0.2)	1	0		
Angina Pectoris	0			1	(0.2)	1
Cardiomyopathy	0			0		
Diastolic Dysfunction	0			1	(0.2)	1
Heart Valve Incompetence	0			1	(0.2)	1
Left Ventricular Hypertrophy	0			0		
Mitral Valve Incompetence	0			1	(0.2)	1
Sinus Bradycardia	0			0		
Tachycardia	0			0		
Investigations	4	(0.8)	4	3	(0.6)	3
Ejection Fraction Decreased	3	(0.6)	3	2	(0.4)	2
Ejection Fraction Abnormal	1	(0.2)	1	0		
Electrocardiogram Change	0			1	(0.2)	1

Roche: MO22982/CIL-TS/FINAL/AEC01P.SAS
Produced: 16 March 2016, 11:26

Source: Listing 16.2.7.1
Notes: [1] All Cardiac Adverse Events including Serious Adverse Events are included in summary statistics.
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
[3] If an AE start date is partially or fully missing, and it is unclear during to which treatment period the AE started, the AE has been assigned to all relevant treatment periods.
[4] Table presents number and percentage of patients (n (%)) and number of events (E).
[5] Percentages are based on the number of patients in the respective group.

Global Safety Database

Table 12 Cardiac Dysfunction, Global Safety Database: Summary Tabulation of Adverse Events by SOC

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
System Organ Class	**Preferred Term**					
Cardiac disorders	Acute left ventricular failure	5	5	0.1	5	0.0
	Cardiac dysfunction	347	264	3.9	348	3.4
	Cardiac failure	1496	1460	21.4	1512	14.7
	Cardiac failure acute	49	49	0.7	49	0.5
	Cardiac failure chronic	35	35	0.5	35	0.3
	Cardiac failure congestive	763	770	11.3	770	7.5
	Cardio-respiratory distress	1	1	0.0	1	0.0
	Cardiogenic shock	25	24	0.4	25	0.2
	Cardiomegaly	58	27	0.4	58	0.6
	Cardiopulmonary failure	19	19	0.3	19	0.2
	Chronic left ventricular failure	1	1	0.0	1	0.0
	Cor pulmonale	1	1	0.0	1	0.0
	Cor pulmonale acute	1	1	0.0	1	0.0
	Diastolic dysfunction	44	18	0.3	44	0.4
	Dilatation ventricular	8	7	0.1	8	0.1
	Left ventricular dilatation	22	13	0.2	22	0.2
	Left ventricular dysfunction	615	489	7.2	626	6.1
	Left ventricular enlargement	6	2	0.0	6	0.1
	Left ventricular failure	68	66	1.0	68	0.7
	Right ventricular dilatation	2	2	0.0	2	0.0
	Right ventricular dysfunction	3	2	0.0	3	0.0
	Right ventricular enlargement	2	1	0.0	2	0.0
	Right ventricular failure	22	21	0.3	22	0.2

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
	Systolic dysfunction	17	15	0.2	17	0.2
	Ventricular compliance decreased	2	0	0.0	2	0.0
	Ventricular dysfunction	38	34	0.5	38	0.4
	Ventricular failure	1	1	0.0	1	0.0
Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema	37	35	0.5	37	0.4
	Dyspnoea paroxysmal nocturnal	7	2	0.0	7	0.1
	Lower respiratory tract congestion	7	1	0.0	7	0.1
	Nocturnal dyspnoea	6	3	0.0	6	0.1
	Orthopnoea	15	6	0.1	15	0.1
	Pulmonary congestion	11	6	0.1	11	0.1
	Pulmonary oedema	187	160	2.3	187	1.8
Hepatobiliary disorders	Hepatic congestion	3	2	0.0	3	0.0
General disorders and administration site conditions	Oedema	467	107	1.6	473	4.6
	Oedema due to cardiac disease	2	0	0.0	2	0.0
	Oedema peripheral	739	144	2.1	759	7.4
	Peripheral swelling	620	75	1.1	651	6.3

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
Investigations	Brain natriuretic peptide increased	11	2	0.0	11	0.1
	Cardiac index decreased	2	0	0.0	2	0.0
	Cardiac output decreased	29	18	0.3	29	0.3
	Cardiac ventriculogram abnormal	3	2	0.0	3	0.0
	Cardiothoracic ratio increased	1	0	0.0	1	0.0
	Ejection fraction decreased	4304	2911	42.7	4360	42.5
	N-terminal prohormone brain natriuretic peptide increased	3	1	0.0	3	0.0
	Right ventricular ejection fraction decreased	5	3	0.0	5	0.0
	Stroke volume decreased	2	2	0.0	2	0.0
	Venous pressure jugular increased	2	2	0.0	2	0.0
Total		**N/A**	**6810**	**100.0**	**10262**	**100.0**
Data cutoff: 24 September 2018. Exposure cut-off: 24 September 2018. Comanifestations are counted as AEs						

Table 13 Cardiac Dysfunction, Global Safety Database: Summary Tabulation of Adverse Event by Outcome

	Event outcome									
Preferred Term	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/ Resolved	Recovered/ Resolved With Sequelae	Recovering/ Resolving	Unknown	Total No. AEs
Acute left ventricular failure	0	0	0	1	0	1	0	2	1	5
Acute pulmonary oedema	2	3	0	5	1	17	0	4	5	37
Brain natriuretic peptide increased	0	0	0	1	3	0	0	2	5	11
Cardiac dysfunction	0	0	0	57	184	25	2	23	57	348
Cardiac failure	2	66	0	230	252	359	45	282	276	1512
Cardiac failure acute	0	12	0	3	2	15	1	14	2	49
Cardiac failure chronic	0	1	0	7	5	5	2	7	8	35
Cardiac failure congestive	6	38	10	88	210	152	32	145	89	770
Cardiac index decreased	0	0	0	0	0	0	0	1	1	2
Cardiac output decreased	1	0	0	2	15	3	0	3	5	29
Cardiac ventriculogram abnormal	0	0	0	0	0	2	0	0	1	3
Cardio-respiratory distress	0	0	0	0	0	0	0	1	0	1
Cardiogenic shock	1	9	0	3	1	4	2	2	3	25
Cardiomegaly	1	0	1	16	18	3	1	2	16	58
Cardiopulmonary failure	0	12	0	1	1	3	0	2	0	19
Cardiothoracic ratio increased	0	0	0	1	0	0	0	0	0	1
Chronic left ventricular failure	0	0	0	0	0	0	0	0	1	1
Cor pulmonale	0	0	0	0	1	0	0	0	0	1
Cor pulmonale acute	0	0	0	0	1	0	0	0	0	1
Diastolic dysfunction	0	0	0	10	16	9	0	2	7	44
Dilatation ventricular	0	0	1	2	3	0	0	0	2	8
Dyspnoea paroxysmal nocturnal	1	0	0	0	4	0	0	1	1	7
Ejection fraction decreased	6	11	13	582	1317	945	27	354	1105	4360

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/ Resolved	Recovered/ Resolved With Sequelae	Recovering/ Resolving	Unknown	
Hepatic congestion	0	0	0	1	0	0	0	0	2	3
Left ventricular dilatation	0	0	0	5	10	4	0	1	2	22
Left ventricular dysfunction	3	2	2	98	188	216	11	54	52	626
Left ventricular enlargement	0	0	0	2	2	0	0	1	1	6
Left ventricular failure	0	2	1	15	4	12	2	22	10	68
Lower respiratory tract congestion	0	0	0	0	4	0	0	1	2	7
N-terminal prohormone brain natriuretic peptide increased	0	0	0	0	2	0	0	0	1	3
Nocturnal dyspnoea	0	0	0	1	2	2	0	0	1	6
Oedema	1	2	2	105	134	110	1	61	57	473
Oedema due to cardiac disease	0	0	0	0	2	0	0	0	0	2
Oedema peripheral	7	0	12	168	217	159	0	121	75	759
Orthopnoea	3	0	0	0	5	4	1	1	1	15
Peripheral swelling	3	2	8	162	273	88	3	47	65	651
Pulmonary congestion	0	0	0	1	1	4	0	1	4	11
Pulmonary oedema	7	10	4	26	31	47	2	31	29	187
Right ventricular dilatation	0	0	0	2	0	0	0	0	0	2
Right ventricular dysfunction	0	0	0	0	1	1	0	1	0	3
Right ventricular ejection fraction decreased	0	0	0	2	2	1	0	0	0	5
Right ventricular enlargement	0	0	0	0	2	0	0	0	0	2
Right ventricular failure	0	4	0	1	4	5	0	6	2	22
Stroke volume decreased	0	0	0	0	1	0	0	0	1	2
Systolic dysfunction	0	0	0	6	6	2	1	0	2	17
Venous pressure jugular increased	0	0	0	2	0	0	0	0	0	2

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/ Resolved	Recovered/ Resolved With Sequelae	Recovering/ Resolving	Unknown	
Ventricular compliance decreased	0	0	0	0	0	0	0	1	1	2
Ventricular dysfunction	0	1	0	9	7	8	2	5	6	38
Ventricular failure	0	0	0	0	0	0	0	1	0	1
Total	**44**	**175**	**54**	**1615**	**2932**	**2206**	**135**	**1202**	**1899**	**10262**
Data cutoff: 24 September 2018. Exposure cut-off: 24 September 2018. Comanifestations are counted as AE										

Table 14 Cardiac Dysfunction, Global Safety Database: Summary Tabulation of Event Outcome by Action Taken

Outcome	Coman	Dose Increased	Dose Interrupted	Dose Modified NOS	Dose Not Changed	Dose Reduced	Drug Withdrawn	Infusion Rate Decreased	Not Applicable	Unknown	Total No. Drug Events
Coman	44	0	0	0	0	0	0	0	0	0	44
Fatal	0	0	2	0	7	0	33	0	101	32	175
Not Applicable	0	0	0	0	1	0	0	0	51	2	54
Not Recovered/Not Resolved	0	0	140	0	317	3	616	2	168	390	1636
Not Reported	0	1	240	1	105	5	552	0	80	1979	2963
Recovered/Resolved	0	0	335	1	345	10	887	1	168	482	2229
Recovered/Resolved With Sequelae	0	0	14	0	15	1	63	0	30	14	137
Recovering/Resolving	0	0	127	0	153	5	523	0	125	278	1211
Unknown	0	0	84	1	131	4	793	0	103	785	1901
Total	**44**	**1**	**942**	**3**	**1074**	**28**	**3467**	**3**	**826**	**3962**	**10350**

Data cutoff: 24 September 2018. Exposure cut-off: 24 September 2018. Comanifestations are counted as AEs

1.3 SEVERITY AND NATURE OF RISK

Metastatic Breast Cancer

- **M77001**

Eight Grade 3 AEs (8.5%) in the docetaxel alone arm and four (4.3%) in the trastuzumab + docetaxel arm were reported. No Grade 4 or 5 AEs were reported in either arm (Table 1).

Stratified data:

Age: In the Herceptin containing arm, more Grade 1 AEs were reported in patients with age ≤50 years compared with an age >50 years (34.3% vs. 21.1%); Grade 2 AEs were reported more frequently in the sub-group of patients >50 years (11.4% vs. 22.8%). In the Herceptin containing arm, Grade 3 AEs were only reported in patients with age ≤50 years (2, 5.7%). No Grade 4 or 5 AEs were reported in any arm.

Summary: No discernible pattern seen in either of the age groups

- BO16216

Across the two treatment arms of anastrozole alone and anastrozole + trastuzumab, cardiac AEs were mainly mild-to-moderate in severity (23/29). Four Grade 3 AEs (3.8%) were reported in the anastrozole alone arm and two Grade 3 AEs (1.9%) were reported in the anastrozole plus trastuzumab arm (Table 2).

Stratified data:

Age:

In patients ≤50 years of age the cardiac events of any grade were reported as follows:

Arimidex arm: 1/32 (3.1%)

Arimidex + Herceptin: 3/27 (11.1%)

Arimidex alone after start of Herceptin: 3/18 (16.7%).

In patients >50 years of age:

Arimidex: 1/72 (1.4%)

Arimidex + Herceptin: 9/76 (11.8%)

Arimidex alone after start of Herceptin: 5/40 (12.5%).

Most cardiac events reported in age ≤50 years were of Grade 2, while those in age group >50 years were predominantly Grade 1 events. No Grade 4 or 5 events were reported in any of the age groups.

A meaningful interpretation of the data is impacted by low event counts across both groups.

Early Breast Cancer (EBC)

Adjuvant Treatment in EBC

- **(BCIRG 006) (H2296s)/GO00773**

Please refer to Table 6 to Table 10.

Stratified data:

Age: The data was stratified for Age with subgroup ≤50 years and >50 years.

Across all the treatment arms, patients in age group >50 years reported higher percentage of "Any symptomatic or clinical significant asymptomatic cardiac events" (all assessment), compared with age group ≤50 years:

AC—>T (27/456, 5.9% vs. 21/594, 3.5%)

AC—>TH (63/476, 13.2% vs. 57/592, 9.6%)

TCH (24/448, 5.4% vs. 28/608, 4.6%)

Region:

The regional data was available for following five regions: Asia (no of patients, n=157), Europe (n=1352), Middle east (n=122), North America (n=1106), Oceania (n=324), South Africa (n=48), and South America (n=65). All cardiac events were compared across these regions.

AC—>T:

- Asia (13/56, 23.2%; Grade 3-4: 1/56, 1.8%)
- Europe (146/454, 32.2% Grade 3-4: 15/454, 3.3%)
- Middle East (17/44, 38.6%, Grade 3-4: 2/44, 4.5%)
- North America (151/357, 42.3%, Grade 3-4: 21/357, 5.9%)
- Oceania (30/102, 29.4%, Grade 3-4: 1/102, 1.0%)
- South Africa (2/13, 15.4%, Grade 3-4: 0/13 0.0%)

- South America (7/24, 29.2%, Grade 3-4: 1/24, 4.2%).

AC—>TH:

- Asia (18/52, 34.6%; Grade 3-4: 3/52, 5.8%)
- Europe (170/450, 37.8% Grade 3-4: 29/450, 6.4%)
- Middle East (15/41, 36.6%, Grade 3-4: 2/41, 4.9%)
- North America (208/380, 54.7%, Grade 3-4: 27/380, 7.1%)
- Oceania (52/108, 48.1%, Grade 3-4: 8/108, 7.4%)
- South Africa (12/18, 66.7%, Grade 3-4: 1/18, 5.6%)
- South America (11/19, 57.9%, Grade 3-4: 0/19, 0.0%).

TCH:

- Asia (12/49, 24.5%, Grade 3-4: 3/49, 6.1%)
- Europe (177/448, 39.5%, Grade 3-4: 28/448, 6.3%)
- Middle East (13/37, 35.1%, Grade 3-4: 0/37, 0.0%)
- North America (179/369, 48.5%, Grade 3-4: 29/369, 7.9%)
- Oceania (49/114, 43%, Grade 3-4: 12/114, 10.5%)
- South Africa (8/17, 47.1%, Grade 3-4: 3/17, 17.6%)
- South America (10/22, 45.5%, Grade 3-4: 1/22, 4.5%).

Summary

In AC—>T arm, the highest percentage of cardiac events were reported in North American patients, followed by Middle Eastern and European. In the AC—>TH arm, the highest percentage of cardiac events were observed in South African patients, followed by South American and North American patients. In the TCH arm, the highest percentages of cardiac events were observed in North American patients, followed by South Africa and South America. The number of Grade 3-4 events reported was low and precluded meaningful comparison between the sub groups.

There was no discernible pattern observed in the Herceptin containing treatment arms across region.

- **BO16348 (HERA):**

10-year median follow-up HERA data

Across the three study arms, AEs within the cardiac dysfunction risk were mainly mild-to-moderate in severity, comprising Grades 1 and 2 of severity (refer to Table 15). In all of the clinical trial arms, the most commonly occurring Grade 1 and Grade 2 AEs were Oedema Peripheral, Cardiac Failure congestive and Ejection Fraction decreased. No Grade 3 AEs were reported in the Observation arm. Cardiac Failure congestive was the

most common Grade 3 AE in all of the trastuzumab-containing arms: trastuzumab 1-year: 13/1682 (0.8%) patients; trastuzumab 2-year: 10/1673 (0.6%) patients. The other Grade 3 AEs in the trastuzumab-containing arms occurred at a frequency of < 0.1%. The most commonly occurring Grade 4 AE was Cardiac Failure congestive and it was observed in the trastuzumab 1-year and 2-year arms (4/1682 (0.2%) and 8/1673 (0.5%) patients, respectively), as well as the Observation only arm (1/1744 (0.1%) patients).

Stratified data:

Age ≤50 years

- Observation only arm: 5.3% (51/959) patients reported a total 57 AEs. All were Grade 1 events (n=48 in 43 patients) and Grade 2 events (n=9 in 9 patients). No Grade 3 and Grade 4 events were reported.
- Herceptin 1-year arm: 16.2% (153/947) patients reported a total of 172 AEs. Majority were Grade 1 events (n= 114 in 106 patients) and Grade 2 events (n=48 in 47 patients). Nine Grade 3 events in 9 patients (Cardiac failure congestive [n=7], one event each of peripheral oedema and ejection fraction decreased) were reported and one Grade 4 event of cardiac failure congestive was reported.
- Herceptin 2-year arm: 18.6% (172/926) patients reported a total of 200 AEs. Majority were Grade 1 events (n=149 in 134 patients) and Grade 2 (n=42 in 41 patients). There were five Grade 3 events in 5 patients (cardiac failure congestive [n=3] and one event each of peripheral oedema and ejection fraction decreased) and 4 events of Grade 4 cardiac failure congestive were reported in 4 patients.

Age >50 years

Observation only arm: 6.9% (54/785) patients reported a total of 57 events. Majority were reported as Grade 1 (n=42 in 41 patients), and Grade 2 (n=14 in 14 patients). One event of cardiac failure congestive was reported as Grade 4 event. No Grade 3 event was reported.

Herceptin 1-year arm: 19.0% (140/735) patients reported a total of 153 events. Majority were reported as Grade 1 (n=102 in 96 patients), Grade 2 (n=38 in 38 patients). Seven Grade 3 events in 7 patients, cardiac failure congestive [n=6] and one event of cardiac failure chronic), and 4 Grade 4 events in 4 patients (3 events of cardiac failure congestive and one event of cardiac failure) were reported.

Herceptin 2-year arm: 21.2% (158/747) patients reported a total of 187 events. Majority were reported as Grade 1 (n=118 in 106 patients), Grade 2 (n=56 in 52 patients). Seven Grade 3 events of cardiac failure congestive reported in 7 patients and 5 Grade 4 events in 4 patients (cardiac failure congestive[n=4] and pulmonary oedema [n=1]) were reported.

Summary

The >50 years subgroup reported higher percentage of patients with AEs compared with the ≤50 years subgroup in all the three arms. For all age groups, majority of the AEs were either Grade 1 or 2 in line with the unstratified outputs.

Table 15 Cardiac Dysfunction, Severity & Frequency: BO16348

sel5_card Summary of Cardiotoxicity, Severity (NCI-CTC Grade) and Frequency, by Body System, Trial treatment (Safety Population)
Protocol(s): BO16348
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	Observation Only N = 1744					Herceptin 1 Year N = 1682					Herceptin 2 Year N = 1673				
	Grade: Total	1 No.	2 No.	3 No.	4 No.	Grade: Total	1 No.	2 No.	3 No.	4 No.	Grade: Total	1 No.	2 No.	3 No.	4 No.
ALL BODY SYSTEMS															
Total Pts with at Least one AE	105	84	23	-	1	293	202	85	16	5	330	240	93	12	8
Total Number of AEs	114	90	23	-	1	325	216	86	16	5	387	267	98	12	9
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS															
Total Pts With at Least one AE	73	61	13	-	-	132	97	37	1	-	147	116	30	1	-
OEDEMA PERIPHERAL	49	38	11	-	-	82	60	21	1	-	101	79	20	1	-
PERIPHERAL SWELLING	17	16	1	-	-	33	22	11	-	-	25	21	4	-	-
OEDEMA	10	9	1	-	-	23	18	5	-	-	27	21	6	-	-
Total Number of AEs	76	63	13	-	-	138	100	37	1	-	153	121	30	1	-
CARDIAC DISORDERS															
Total Pts With at Least one AE	24	15	8	-	1	115	62	36	14	5	157	96	47	10	8
CARDIAC FAILURE CONGESTIVE	19	14	4	-	1	96	48	31	13	4	146	89	39	10	8
CARDIAC FAILURE CHRONIC	2	-	2	-	-	11	6	4	1	-	6	4	2	-	-
LEFT VENTRICULAR DYSFUNCTION	-	-	-	-	-	6	5	1	-	-	9	4	5	-	-
CARDIAC FAILURE	1	1	-	-	-	2	1	-	-	1	-	-	-	-	-
CARDIOMEGALY	1	-	1	-	-	1	1	-	-	-	-	-	-	-	-
DIASTOLIC DYSFUNCTION	-	-	-	-	-	1	1	-	-	-	1	1	-	-	-
LEFT VENTRICULAR FAILURE	1	-	1	-	-	-	-	-	-	-	1	-	1	-	-
VENTRICULAR DYSFUNCTION	-	-	-	-	-	1	1	-	-	-	-	-	-	-	-
Total Number of AEs	24	15	8	-	1	118	63	36	14	5	163	98	47	10	8
INVESTIGATIONS															
Total Pts With at Least one AE	13	11	2	-	-	69	53	13	1	-	68	46	21	1	-
EJECTION FRACTION DECREASED	13	11	2	-	-	69	53	13	1	-	68	46	21	1	-
CARDIOTHORACIC RATIO INCREASED	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-
Total Number of AEs	13	11	2	-	-	69	53	13	1	-	69	47	21	1	-

Investigator text for Adverse Events encoded using MedDRA version 18.0.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
AE15 31MAR2016:13:19:04 (1 of 2)

Race:

Observation arm:

- Black: 2/6 (33.3%) patients reported 2 events (no Grade 3 and Grade 4 events reported)
- Caucasian: 85/1453 (5.8%) patients reported 93 events (Grade 4: 1 event and no Grade 3 event)
- Oriental: 15/218 (6.9%) patients reported 16 events (no Grade 3 and Grade 4 events reported)
- Other: 3/67 (4.5%) patients reported 3 events (no Grade 3 and Grade 4 events reported)

Herceptin 1-year arm:

- Black: 3/8 (37.5%) patients reported 3 events (Grade 3: 1 event and no Grade 4 event)
- Caucasian: 257/1404(18.3%) patients reported 289 events (Grade 3: 14, Grade 4: 4 events)
- Oriental: 22/213 (10.3%) patients reported 22 events (one Grade 3 event, no Grade 4 events)
- Other: 11/57 (19.3%) patients reported 11 events (no Grade 3 and one Grade 4 event)

Herceptin 2-year arm:

- Black: 1/5 (20.0%) patients reported 1 event (no Grade 3 and Grade 4 events reported)
- Caucasian: 279/1397(20.0%) patients reported 324 events (Grade 3: 11, Grade 4: 8 events)
- Oriental: 36/213 (16.9%) patients reported 46 events (one event each of Grade 3 and Grade 4 were reported)
- Other: 14/58 (24.1%) patients reported 16 events (no Grade 3 and Grade 4 events were reported)

Summary

Majority of the patients included in the trials were Caucasian. Across all the race sub-groups, majority of the events reported were Grade 1 and Grade 2. A meaningful interpretation of the data is impacted by low event counts across other race sub-groups.

- **MO28048 (SafeHER)**

Overall, the cardiac dysfunction risks were mainly mild-to-moderate in severity, comprising of Grades 1 and 2 events. The most commonly occurring Grade 1 AEs were oedema peripheral, peripheral swelling and ejection fraction decreased. The most commonly occurring Grade 2 AEs were ejection fraction decreased and oedema peripheral. Cardiac failure congestive and ejection fraction decreased were the most commonly occurring Grade 3 events. Cardiac failure congestive and pulmonary oedema were the Grade 4 events.

No Grade 5 fatal events were reported.

Age ≤65 years

- 17.0% (365 out of 2141) patients reported a total of 419 AEs. Majority were Grade 1 events (n=277 in 245 patients) and Grade 2 (n=118 in116 patients). There were 22 Grade 3 events in 22 patients (left ventricular dysfunction and ejection fraction decreased [n=7 each] and cardiac failure congestive [n=6] and one event each of oedema peripheral and oedema) and two Grade 4 events (cardiac failure congestive and pulmonary oedema) were reported in one patient. No Grade 5 events were reported.

Age >65 years

- 19.2% (83 out of 432) patients reported a total of 102 AEs. Majority were Grade 1 events (n=72 in 61 patients) and Grade 2 (n=26 in 26 patients). There were four Grade 3 events in four patients (cardiac failure congestive and ejection fraction decreased [n=2 each]). No Grade 4 and 5 events were reported.

Summary

The >65 years sub-group reported higher percentage of patients with AEs compared with the ≤65 years sub-group. For all age groups, majority of the AEs were either Grade 1 or 2 in line with the unstratified outputs.

Race

White: 355/1977 (18.0%) patients reported 416 events (Grade 3:19 events, no Grade 4 and 5 events were reported)

Black: 9/31(29.0%) patients reported 13 events (Grade 3: 4 events, no Grade 4 and 5 events were reported)

Asian: 46/378 (12.2%) patients reported 48 events (Grade 3: 3 events, Grade 4: 2 events and no Grade 5 event)

Other: 20/89 (22.5%) patients reported 23 events (no grade 3, 4 or 5 events)N/A (per local regulation): 15/89 (16.9%) patients reported 17 events (no grade 3, 4 or 5 events)

Unknown: 3/9 (33.3%) patients reported 4 events (no grade 3, 4 or 5 events)

Summary

Majority of the patients included in the trials were White. Across all the race sub-groups, majority of the events reported were Grade 1 and Grade 2

Joint Analysis of NSABP B-31 and N9831

Of the Cardiac dysfunction AEs (as defined in this RMP), only severity data on Cardiac – left ventricular function and Oedema were collected for both Studies B-31 and N9831, i.e., no severity data was collected for CHF, decreased (LV)EF, or other Cardiac failure SMQ AEs.

For Cardiac – left ventricular function, the distribution of Grades 3-5 AEs during Periods 2-4 (defined as any time after the initiation of paclitaxel therapy) in AE-Evaluable patients in the Joint Analysis data were as follows:

- AC->T: 1 (0.1%)
- AC ->T+H: 42 (2.1%)
- AC->T->H: 3 (0.8%)

For Cardiac – left ventricular function, the distribution of Any Grade AEs were as follows:

- AC->T: 28 (1.9%)
- AC ->T+H: 262 (13.1%)
- AC->T->H: 27 (7.6%)

For Oedema, the distribution of Grades 3-5 AEs were as follows:

- AC->T: 1 (0.1%)
- AC ->T+H: 0 (0.0%)
- AC->T->H: 0 (0.0%)

For Oedema, the distribution of Any Grade AEs was as follows:

- AC->T: 25 (1.7%)
- AC ->T+H: 43 (2.2%)
- AC->T->H: 4 (1.1%).

A total of three cardiac deaths were observed in the trastuzumab-containing arms compared with five cardiac deaths in the control arm. These cardiac deaths did not necessarily include CHF (i.e., the category of cardiac death in the Joint Analysis included MI, arrhythmia, and sudden death).

Stratified data

The AEs of cardiac dysfunction were stratified by the presence of number of known risk factors (age >50 years, use of anti−hypertensive medications at baseline, and LVEF at paclitaxel baseline ≤55%), and by race.

In this study, majority of patients were White. Other substantial groups included were Black and Hispanic. Most of these patients were in the AC –>T or AC –>T+H arm. The stratification by race, in patients with 0, 1, 2, or all the 3 of these risk factors is presented below:

Patients with no risk factors:

AC –> T arm:

- Asian (0/8, 0.0%)
- Hispanic (0/26, 0.0%)
- Pacific Islander (0/5, 0.5%)
- White (2/392, 0.5%)
- Black (0/34, 0.0%)
- Unknown (0/2, 0.0%)
- Other (0/3, 0.0%)
- Native American (0/0, 0.0%);

AC –>T+H arm

- Asian patients (1/27, 3.7%)
- Hispanic (0/31, 0.0%)
- Pacific Islander (0/5, 0.0%)
- White patients (7/660, 1.1%)
- Black patients (2/48, 4.2%)
- Unknown (0/3, 0.0%)
- Other (0/8, 0.0%)
- Native American (0/2, 0.0%);

AC –>T –>H arm

- Asian patients (0/4, 0.0%)
- Hispanic (0/5, 0.0%)
- Pacific Islander (0/0, 0.0%)
- White patients (0/102, 0.0%)

- Black patients (0/3, 0.0%)
- Unknown (0/3, 0.0%)
- Other (0/0, 0.0%)
- Native American (0/0, 0.0%);

Patients with one risk factor:

AC –> T arm: Asian (1/11, 9.1%), Hispanic (0/20, 0.0%), Pacific islander (1/6, 16.7%), White (4/421, 1%), Black (1/32, 3.1%), Unknown (0/2, 0.0%), Other (0/2, 0.0%), and Native American (0/2, 0.0%);

AC –>T+H arm: Asian (0/26, 0.0%), Hispanic (0/27, 0.0%), Pacific Islander (0/5, 0.0%), White (24/617, 3.9%), Black (0/39, 0.0%), Unknown (0/6, 0.0%), Other (0/3, 0.0 %), and Native American (0/4, 0.0%);

AC –>T –>H arm: Asian (0/3, 0.0%), Hispanic (1/3, 33.3%), Pacific Islander (0/1, 0.0%), White (2/108, 1.9%), Black (0/7, 0.0%), Unknown (0/0, 0.0%), Other (0/2, 0.0%), and Native American (0/1, 0.0%).

Patients with two risk factors:

AC –> T arm: Asian (0/10, 0.0%), Hispanic (1/10, 10 %), Pacific Islander (0/3, 0.0%), White (3/216, 1.4%), Black (0/33, 0.0%), Unknown (0/0, 0.0%), Other (0/1, 0.0%), and Native American (0/0, 0.0%);

AC –>T+H arm: Asian (2/12 (16.7%), Hispanic (0/12, 0.0%), Pacific Islander (0/1, 0.0%), White (20/302, 6.6%), Black (1/29, 3.4%), Unknown (0/0, 0.0%), Other (0/3, 0.0%), and Native American (0/0, 0.0%);

AC –>T –>H arm: Asian (0/3, 0.0%), Hispanic (0/3, 0.0%), Pacific Islander (0/0, 0.0%), White (2/57 3.5 %), Black (1/7, 14.3%), Unknown (0/0, 0.0%), Other (0/2, 0.0%), and Native American (0/0, 0.0%).

Patients with three risk factors:

AC –> T arm: Hispanic (0/1, 0.0%), White (0/32, 0.0%), Black (0/9, 0.0%), no patient included in any other race

AC –>T+H arm: Asian (0/1, 0.0%); Hispanic (0/2, 0.0%); White (3/34, 8.8%), Black (1/4, 25%), other (0/1, 0.0%), no patient included in any other race

AC –>T –>H arm: White (1/9, 11.1%), Black (0/1, 0.0%), no patient included in any other race.

Summary

A meaningful stratified comparison of cardiac dysfunction by race is impacted by low number of patients and AEs in most of the resulting subgroups.

Neoadjuvant treatment in EBC

MO16432 (NOAH)

Cardiac events reported in at least two patients included: angina pectoris (5 patients in each of the HER2-positive arms), tachycardia (5 patients in each of the HER2-positive arms and one patient in the HER2-negative arm) and palpitations (3 patients in each of the HER2-positive arms and one patient in the HER2-negative arm). None of these cardiac events were reported as Grade 3 or 4 AEs. The myocardial ischemia in the HER2+TC arm was of Grade 2 intensity at worst and recovered on the same day without sequelae.

During the post-operative period, 16 patients experienced 22 cardiac AEs (8.9% [10/112] patients with 15 AEs in HER2 positive + TC, 10.0% [2/20] patients with two AEs in HER2 positive + C→T, 5.9% [4/68] patients with five AEs in HER2 positive + C). In the HER2 positive + C arm, patient [redacted] experienced a Grade 3 pericardial effusion and in the HER2 positive + TC arm, patient [redacted] had a Grade 3 decreased ejection fraction considered related to study medication and reported as an SAE.

Neoadjuvant-adjuvant Treatment in EBC:

BO22227 – (HannaH):

Intravenous (Herceptin IV) & Subcutaneous (Herceptin SC) in EBC:

Severity per CTC Grading

In the IV arm, all AEs were either Grade 1 or Grade 2; there were no Grade 3 -5 AEs. In the Herceptin SC arm, 4 AEs in 3 patients were Grade 3 in severity; two of these were assessed as serious. There was no Grade 4 or 5 cardiac dysfunction-related AEs in the Herceptin SC arm. Please refer to Table 5 (IV arm) and Table 6 (SC arm).

Stratified data:

Age:

In the Herceptin IV arm, a higher number of patients aged >50 years, reported cardiac dysfunction-related AEs compared with those ≤50 years (31/143, 22%) vs. 25/155, 16%. In the Herceptin SC arm, the number of patients reporting AEs was lower in patients aged >50 years (19/140, 14%) as compared with ≤50 years (28/157, 18%).

In the Herceptin IV arm, Grade 1 events were reported in 12% and 17% patients in age ⩽50 and >50 years, respectively. In the SC arm, Grade 1 events were reported in 15% and 11% patients in age ⩽50 and >50 years, respectively.

In the Herceptin IV arm, Grade 2 events were reported in 5% and 6% patients in age ≤50 and >50 years, respectively.In the Herceptin SC arm, Grade 2 events were reported in 3% and 2% of the patients in age ≤50 and >50 years sub-groups, respectively.

There were no Grade 3 AEs reported in the Herceptin IV arm, while in the Herceptin SC arm 2 and 1 patient(s) in age group ⩽50 and >50 years reported a Grade 3 AE.

No grade 4 or 5 AEs were reported in any of the patients.

Summary: No clear discernible pattern was observed in either of the age groups for cardiac dysfunction-related events.

Race:

Most of the patients enrolled in the study were 'White' (n=208 in the Herceptin IV arm and n=200 in the Herceptin SC arm) followed by Asians (n=61 in IV vs. n=64 in SC arm) 'Other' race was reported in 29 and 33 patients in the Herceptin IV arm and Herceptin SC arms, respectively.

Asian patients reported more Grade 1 events (IV arm: 15 [25%], and SC arm: 15 [23%]) as compared with White (IV arm: 243 [12%], and SC arm: 208 [10%]) and 'Other' (IV arm: 4 [14%], and SC arm: 2 [6%]). Grade 2 events were comparable across all arms. Grade 3 events were reported in 3 patients in the SC arm (1[<1%] white patient, and 2 patients 6%] in 'Other' race). No Grade 4 or 5 events were reported.

Summary

Asian patients reported more AEs across both the arms, compared with the 'White' and 'Other' race patients, most being of low severity and with a trend for more AEs in the IV arm.

MO22982 (PrefHER)
Results from crossover period SC-IV or IV-SC (479 patients for Herceptin SC period and 478 patients for Herceptin IV period).

Herceptin IV (4 cycles):

Two patients with grade 3 Left Ventricular Dysfunctions were reported. Three patients had three Cardiac AEs of Grade 2 severity and eleven had 12 Grade 1 AEs.

Herceptin SC (4 cycles):

One patient with grade 3 left ventricular dysfunction was reported. Two patients had two Cardiac AEs of a Grade 2 severity and nine patients had 12 Grade 1 AEs. Refer to Table 16 below.

Table 16 Cardiac Dysfunction by Severity MO22982 (Crossover SC-IV / IV-SC, EBC)

Cohort 1 and 2 Maximum CTC grade System Organ Class Preferred Term	SC Period (N=479) n (%)	E	IV Period (N=478) n (%)	E
Maximum CTC grade: 3-Severe				
Cardiac Disorders	1 (0.2)	1	2 (0.4)	2
Left Ventricular Dysfunction	1 (0.2)	1	2 (0.4)	2
Cardiac Failure Congestive	0		0	
Maximum CTC grade: 2-Moderate				
Cardiac Disorders	1 (0.2)	1	3 (0.6)	3
Left Ventricular Dysfunction	0		1 (0.2)	1
Cardiac Failure Congestive	1 (0.2)	1	0	
Angina Pectoris	0		1 (0.2)	1
Bradycardia	0		1 (0.2)	1
Palpitations	0		0	
Maximum CTC grade: 1-Mild				
Cardiac Disorders	6 (1.3)	7	9 (1.9)	9
Palpitations	3 (0.6)	3	2 (0.4)	2
Left Ventricular Dysfunction	1 (0.2)	1	2 (0.4)	2
Bradycardia	1 (0.2)	1	2 (0.4)	2
Cardiac Failure Congestive	1 (0.2)	1	0	
Extrasystoles	1 (0.2)	1	0	
Cardiomyopathy	0		0	
Diastolic Dysfunction	0		1 (0.2)	1
Heart Valve Incompetence	0		1 (0.2)	1
Left Ventricular Hypertrophy	0		0	
Mitral Valve Incompetence	0		1 (0.2)	1
Sinus Bradycardia	0		0	
Tachycardia	0		0	

Notes: [1] All Adverse Events including Serious Adverse Events are included in summary statistics.
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
[3] If an AE start date is partially or fully missing, and it is unclear during to which treatment period the AE started, the AE has been assigned to all relevant treatment periods.
[4] Table presents number and percentage of patients (n (%)) and number of events (E).
[5] Percentages are based on the number of patients in the respective group.

Advanced Gastric Cancer:

BO18255 (ToGA):

Across both treatment arms, cardiac AEs were mostly mild-to-moderate in severity. See

Table 3 for a listing of CTC worst grading severity.

Stratified data:

Age:

Fluoropyrimidine/Cisplatin arm:

- ≤50 (n=69): Grade 1: 3 (4.3%) and Grade 2: 1 (1.4%). No Grade 3 or Grade 4 events were reported.
- 50 (n=221): Grade 1: 27 (12.2%), Grade 2: 7 (3.2%), Grade 3: 2 (0.9%), and Grade 4: 1 (0.5%).

Trastuzumab/Fluoropyrimidine/Cisplatin arm

- ≤50 (n=57): Grade 1: 6 (10.5%), Grade 2: 2 (3.5%), No Grade 3 or Grade 4 events were reported.
- 50 (n=237): Grade 1: 30 (12.7%), Grade 2: 6 (2.5%), and Grade 3 and Grade 4: 2 (0.8%).

Summary:

Treatment with Herceptin increases the risk of cardiac dysfunction. Age >50 years is an identified risk factor for cardiac dysfunction. The stratified data from this study confirms this finding.

Gender:

Male patients:

Fluoropyrimidine/Cisplatin arm:

- Male: (n=218): Grade 1: 18 (8.3%), Grade 2: 2 (0.9%), Grade 3: 1(0.5%), and Grade 4: None.
- Females: (n=72): Grade 1: 12 (16.7%) and Grade 2: 2 (2.8%). No Grade 3 or 4 events were reported.

Trastuzumab/Fluoropyrimidine/Cisplatin arm

- Male: Grade 1: 27 (11.9%), Grade 2: 5 (2.2%), Grade 3: 1 (0.4%), and Grade 4: 4(0.9%).
- Female: (n=68): Grade 1: 9 (13.2%), Grade 2: 3 (4.4%). No Grade 3 and 4 events reported.

Summary

Within respective arms, the percentage of AEs was more in female patients. Although no Grade 3 or 4 AEs were reported in female patients.

Race:

Fluoropyrimidine/Cisplatin arm:

- Caucasians (n=105): Grade 1: 5 (4.8%), Grade 2: 3 (2.9%), Grade 3: 2 (1.9%), and Grade 4: 1 (1%).
- Oriental (n=158): Grade 1: 25 (15.8%), Grade 2: 5 (3.2%). No Grade 3 or 4 AEs were reported.

Trastuzumab/Fluoropyrimidine/Cisplatin arm

- Caucasians (n=115): Grade 1: 7 (6.1%), Grade 2: 4 (3.5%), Grade 3: 1 (0.9%), and no Grade 4 events were reported.
- Oriental (n=151): Grade 1: 24 (15.9%), Grade 2: 1 (1.3%), Grade 3: 1 (0.7%), and Grade 4: 2 (1.3%).

Summary

The Oriental patients reported higher numbers of AEs compared with the Caucasians; majority of them were Grade 1. The meaningful comparison of Grade 2, 3, and 4 events is impacted by low numbers of events reported in each of these sub-groups.

Region:

In the Herceptin containing arm, Asian patients reported the most number of Grade 1 AEs as compared with the European patients (25/164, 16.1% vs. 3/99, 3%). A relatively lower number of Grade 2 (Asia: 3, 1.9%; Europe: 3, 3%), Grade 3 (Asia: 1, 0.6%; Europe: 1, 1%), and Grade 4 (Asia: 2[1.3%], Europe: none) events were reported precluding a meaningful analysis.

1.4 RISK GROUPS OR RISK FACTORS

Table 17 Incidence of Cardiac Events by risk factor Subgroup in the AC→T and AC→TH Arms: Safety Population (BCIRG 006) (H2296s)/GO00773

	Number of Patients with Cardiac Events per Arm		
Subgroup	AC→T	AC→TH	p-value[a]
Age (yr)			
n	1050	1068	—
≤50	2/594 (0.3%)	8/592 (1.4%)	0.0560
>50	4/456 (0.9%)	15/476 (5.4%)	0.0141
Prior or current use of cardiovascular medications at baseline			
n	1050	1068	—
Yes	3/178 (1.7%)	7/186 (3.8%)	0.2253
No	3/872 (0.3%)	16/882 (1.8%)	0.0029
Hypertension at baseline			
n	1050	1068	
Yes	1/182 (0.5%)	7/188 (3.7%)	0.0359
No	5/868 (0.6%)	16/880 (1.8%)	0.0172
Lowest post-baseline LVEF			
n	1015	1041	—
>60%	0/4 (0.0%)	0/0 (0.0%)	NE
70%–79%	0/72 (0.0%)	0/39 (0.0%)	NE
60%–69%	0/397 (0.0%)	2/355 (0.6%)	0.1343
<60%	6/542 (1.1%)	21/647 (3.2%)	0.0137

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; LVEF = left ventricular ejection fraction; NE = not estimable; TCH = docetaxel, carboplatin, and Herceptin.

[a] Derived from the Pearson χ^2 test.

Table 18 Time to First Cardiac or LVEF Event following Initiation of Docetaxel or Trastuzumab Therapy, AC→T versus AC→TH (BCIRG 006) (H2296s)/GO00773

Covariate [a]	No. of Observations Used	No. of Events	Hazard Ratio		
			Estimate	95% CI	p-value [b]
Treatment [c]	2066	156	2.38	(1.679, 3.383)	<0.0001
0=AC→T					
1=AC→TH					
Age (yr)	2066	156	1.55	(1.131, 2.135)	0.0067
0=≤50					
1=>50					
Nodal status	2066	156	0.98	(0.694, 1.395)	0.9288
0=Negative					
1=Positive					
Prior or current cardiovascular medications at baseline	2066	156	0.83	(0.531, 1.286)	0.3982
0=No					
1=Yes					
Hypertension ongoing at baseline	2066	156	0.85	(0.550, 1.312)	0.4614
0=No					
1=Yes					
Karnofsky performance status	2066	156	1.22	(0.841, 1.771)	0.2950
0=100					
1=<100					
Radiation to left side of the chest	2066	156	1.17	(0.838, 1.632)	0.3573
0=No					
1=Yes					
Absolute decline of >15 points in LVEF	2066	156	5.99	(1.909, 18.812)	0.0022
0=No					
1=Yes					
Baseline LVEF	2065	156	1.01	(0.900, 1.031)	0.3251
LVEF at T, TH, TCH baseline	2064	156	0.96	(0.944, 0.984)	0.0005
LVEF ≥28 days prior to event (continuous time-dependent covariate) [d]	2066	156	0.94	(0.916, 0.956)	<0.0001
LVEF value <55% at least 28 days prior to event [d]	2066	156	3.22	(2.258, 4.594)	<0.0001
0=No					
1=Yes					

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; LVEF=left ventricular ejection fraction; TCH=docetaxel, carboplatin, and Herceptin.

[a] 0 and 1 indicate coding of variable in the Cox proportional hazards model.

[b] Wald p-value associated with estimated hazard ratio.

[c] All models include indicator variable for treatment.

[d] Time-varying covariate.

Table 19 presents the actual numbers and percentages of patients with a cardiac event in each risk category: age > 50 years, the use of anti-hypertensive medications at baseline, and LVEF at paclitaxel baseline ≤55%. This table illustrates how the incidence of cardiac events in the AC→T + H group was influenced by these factors. Note that, when LVEF at paclitaxel baseline ≤55% and either age > 50 years or use of anti-hypertensive medications at baseline, the incidence of cardiac events in the AC→T + H patients was > 9.5%. In addition, when LVEF at paclitaxel baseline ≤55% and age > 50 years, the incidence of cardiac events in the AC→T + H group was > 9.2% and in the AC→T→H group was >12.5%. It should be noted that some of these percentages were based on small numbers of events in relatively few patients.

Table 20 presents the incidence of cardiac events by the number of risk factors following initiation of paclitaxel or Herceptin + paclitaxel Therapy. The risk factors considered were age >50 years, the use of anti-hypertensive medication, and LVEF ≤55%.

In the AC→T + H group, the risk of a cardiac event increased with the number of risk factors present, from an incidence of 1.3% when no risk factors were present to 9.5% when all three risk factors were present. In the AC→T→H group, the incidence of a cardiac event was 4.2% when any two of the three risk factors were present and 10.0% (1/10) when all three risk factors were presented. The incidence of a cardiac event was 1.5% when any two of the three risk factors were present in AC→T patients.

Table 19 Rates of Cardiac Events by Risk Factor: Patients from the Joint Safety Population with Follow-Up after Paclitaxel Baseline (Joint Analysis: B-31; N9831)

Age > 50	Use of Hypertension Medications at Baseline	LVEF at Paclitaxel Baseline <=55	AC->T	AC->T+H	AC->T->H
Yes	Yes	Yes	0/ 42 (0.0%)	4/ 42 (9.5%)	1/ 10 (10.0%)
		No	0/ 148 (0.0%)	12/ 245 (4.9%)	1/ 50 (2.0%)
	No	Yes	4/ 111 (3.6%)	9/ 98 (9.2%)	2/ 16 (12.5%)
		No	3/ 301 (1.0%)	16/ 483 (3.3%)	2/ 79 (2.5%)
No	Yes	Yes	0/ 14 (0.0%)	2/ 16 (12.5%)	0/ 6 (0.0%)
		No	0/ 45 (0.0%)	1/ 75 (1.3%)	0/ 12 (0.0%)
	No	Yes	4/ 150 (2.7%)	7/ 169 (4.1%)	1/ 34 (2.9%)
		No	2/ 470 (0.4%)	10/ 784 (1.3%)	0/ 114 (0.0%)

A=doxorubicin; C=cyclophosphamide; H=Herceptin; LVEF=left ventricular ejection fraction; T=paclitaxel;

Source: Biostatistics([redacted]) pgm(/immuno/her2/abcjoint/finalos/programs/t_cardiac_rates_hypt) output (t_cardiac_rates_hypt)
Database(Data Received in 2013) Datasets (patcard)
Joint Analysis Final Overall Survival : Generated 17JUL13 12:26 Page 1 of 1

Table 20 Rates of Cardiac Events by Number of Risk Factors following Initiation of Paclitaxel or Herceptin + Paclitaxel Therapy: Patients from the Joint Safety Population with Follow-Up after Paclitaxel Baseline (Joint Analysis: B-31; N9831)

Number of patients with an event/ number of patients per risk factor subset (percent)
(95% CI for the binomial proportion x 100%)

Number of Risk Factors *	AC->T	AC->T+H	AC->T->H
0	2/ 470 (0.4%) (0.0%, 1.0%)	10/ 784 (1.3%) (0.5%, 2.1%)	0/ 114 (0.0%) (100.0%, 100.0%)
1	7/ 496 (1.4%) (0.4%, 2.4%)	24/ 727 (3.3%) (2.0%, 4.6%)	3/ 125 (2.4%) (0.0%, 5.1%)
2	4/ 273 (1.5%) (0.0%, 2.9%)	23/ 359 (6.4%) (3.9%, 8.9%)	3/ 72 (4.2%) (0.0%, 8.8%)
3	0/ 42 (0.0%) (100.0%, 100.0%)	4/ 42 (9.5%) (0.6%, 18.4%)	1/ 10 (10.0%) (0.0%, 28.6%)

A=doxorubicin; C=cyclophosphamide; CI=confidence interval; H=Herceptin; T=paclitaxel;
* The risk factors are: age > 50 years, use of anti-hypertensive medications at baseline, and non-missing LVEF at paclitaxel baseline <= 55.

Source: Biostatistics([redacted]) pgm(/immuno/her2/abcjoint/finalos/programs/t_cardiac_risk_hypt) output (t_cardiac_risk_hypt)
Database(Data Received in 2013) Datasets (patcard)
Joint Analysis Final Overall Survival : Generated 17JUL13 12:27 (PDRD)

2. ADMINISTRATION-RELATED REACTIONS

Table 21 Administration Related Reactions by System Organ Class and Preferred Term - Whole Study, Reduced Event Count

(Safety Population)

System Organ Class Preferred Term	Cohort A (N=1864) n	(%)	E	Cohort B (N=709) n	(%)	E	Overall (N=2573) n	(%)	E
Number of Administration Related Reactions	743	(39.9)	1087	277	(39.1)	407	1020	(39.6)	1494
Skin And Subcutaneous Tissue Disorders	421	(22.6)	503	173	(24.4)	205	594	(23.1)	708
Rash	183	(9.8)	183	74	(10.4)	74	257	(10.0)	257
Erythema	159	(8.5)	159	75	(10.6)	75	234	(9.1)	234
Pruritus	116	(6.2)	116	35	(4.9)	35	151	(5.9)	151
Urticaria	19	(1.0)	19	8	(1.1)	8	27	(1.0)	27
Rash Pruritic	6	(0.3)	6	4	(0.6)	4	10	(0.4)	10
Pruritus Generalised	8	(0.4)	8	1	(0.1)	1	9	(0.3)	9
Rash Erythematous	3	(0.2)	3	5	(0.7)	5	8	(0.3)	8
Rash Generalised	3	(0.2)	3	2	(0.3)	2	5	(0.2)	5
Swelling Face	4	(0.2)	4	0		0	4	(0.2)	4
Generalised Erythema	1	(0.1)	1	1	(0.1)	1	2	(0.1)	2
Pruritus Allergic	1	(0.1)	1	0		0	1	(0.0)	1
Respiratory, Thoracic And Mediastinal Disorders	314	(16.8)	349	104	(14.7)	113	418	(16.2)	462
Cough	197	(10.6)	197	57	(8.0)	57	254	(9.9)	254
Dyspnoea	123	(6.6)	123	48	(6.8)	48	171	(6.6)	171
Asthma	12	(0.6)	12	4	(0.6)	4	16	(0.6)	16
Sneezing	5	(0.3)	5	1	(0.1)	1	6	(0.2)	6
Wheezing	4	(0.2)	4	2	(0.3)	2	6	(0.2)	6
Respiratory Failure	2	(0.1)	2	0		0	2	(0.1)	2
Bronchospasm	1	(0.1)	1	0		0	1	(0.0)	1

Roche: M028048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/AECRI2XP.SAS
Produced: 19 February 2016, 11:43

Source: Listing 16.2.7.8
Notes: [1] Administration Related Reaction is defined as all events based on a MedDRA basket
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count
[3] Table presents number and percentage of patients (n (%)) and number of events (E)
[4] Percentages are based on the number of patients in the respective group
[5] Only one event is counted for multiple occurrences of the same AE (preferred term) in a patient

Table 14.3.5.9.10.1b Administration Related Reactions by System Organ Class and Preferred Term - Whole Study, Reduced Event Count (Safety Population)

System Organ Class Preferred Term	Cohort A (N=1864) n (%)	E	Cohort B (N=709) n (%)	E	Overall (N=2573) n (%)	E
Respiratory, Thoracic And Mediastinal Disorders (contd ...)						
Choking	1 (0.1)	1	0	0	1 (0.0)	1
Hyperventilation	1 (0.1)	1	0	0	1 (0.0)	1
Laryngeal Oedema	0	0	1 (0.1)	1	1 (0.0)	1
Nasal Obstruction	1 (0.1)	1	0	0	1 (0.0)	1
Respiratory Distress	1 (0.1)	1	0	0	1 (0.0)	1
Throat Tightness	1 (0.1)	1	0	0	1 (0.0)	1
Vascular Disorders	66 (3.5)	69	28 (3.9)	29	94 (3.7)	98
Flushing	46 (2.5)	46	22 (3.1)	22	68 (2.6)	68
Hypotension	22 (1.2)	22	7 (1.0)	7	29 (1.1)	29
Circulatory Collapse	1 (0.1)	1	0	0	1 (0.0)	1
General Disorders And Administration Site Conditions	60 (3.2)	62	21 (3.0)	22	81 (3.1)	84
Oedema	22 (1.2)	22	11 (1.6)	11	33 (1.3)	33
Chest Discomfort	17 (0.9)	17	5 (0.7)	5	22 (0.9)	22
Face Oedema	13 (0.7)	13	1 (0.1)	1	14 (0.5)	14
Swelling	6 (0.3)	6	4 (0.6)	4	10 (0.4)	10
Injection Site Hypersensitivity	3 (0.2)	3	1 (0.1)	1	4 (0.2)	4
Sensation Of Foreign Body	1 (0.1)	1	0	0	1 (0.0)	1

Roche: M028048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/AECRI2XP.SAS
Produced: 19 February 2016, 11:43

Source: Listing 16.2.7.8
Notes: [1] Administration Related Reaction is defined as all events based on a MedDRA basket
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count
[3] Table presents number and percentage of patients (n (%)) and number of events (E)
[4] Percentages are based on the number of patients in the respective group
[5] Only one event is counted for multiple occurrences of the same AE (preferred term) in a patient

Table 14.3.5.9.10.1b Administration Related Reactions by System Organ Class and Preferred Term - Whole Study, Reduced Event Count (Safety Population)

System Organ Class Preferred Term	Cohort A (N=1864) n (%)	E	Cohort B (N=709) n (%)	E	Overall (N=2573) n (%)	E
Immune System Disorders	54 (2.9)	54	18 (2.5)	20	72 (2.8)	74
Hypersensitivity	34 (1.8)	34	13 (1.8)	13	47 (1.8)	47
Drug Hypersensitivity	16 (0.9)	16	6 (0.8)	6	22 (0.9)	22
Anaphylactic Reaction	2 (0.1)	2	0	0	2 (0.1)	2
Anaphylactic Shock	1 (0.1)	1	1 (0.1)	1	2 (0.1)	2
Allergic Oedema	1 (0.1)	1	0	0	1 (0.0)	1
Injury, Poisoning And Procedural Complications	30 (1.6)	30	7 (1.0)	7	37 (1.4)	37
Infusion Related Reaction	30 (1.6)	30	7 (1.0)	7	37 (1.4)	37
Eye Disorders	12 (0.6)	13	8 (1.1)	8	20 (0.8)	21
Eye Pruritus	3 (0.2)	3	2 (0.3)	2	5 (0.2)	5
Eye Swelling	3 (0.2)	3	1 (0.1)	1	4 (0.2)	4
Ocular Hyperaemia	2 (0.1)	2	2 (0.3)	2	4 (0.2)	4
Eye Oedema	1 (0.1)	1	2 (0.3)	2	3 (0.1)	3
Eyelid Oedema	2 (0.1)	2	1 (0.1)	1	3 (0.1)	3
Periorbital Oedema	2 (0.1)	2	0	0	2 (0.1)	2
Gastrointestinal Disorders	4 (0.2)	4	2 (0.3)	2	6 (0.2)	6
Lip Swelling	2 (0.1)	2	0	0	2 (0.1)	2
Tongue Oedema	1 (0.1)	1	1 (0.1)	1	2 (0.1)	2
Oedema Mouth	1 (0.1)	1	0	0	1 (0.0)	1
Swollen Tongue	0	0	1 (0.1)	1	1 (0.0)	1

Notes: [1] Administration Related Reaction is defined as all events based on a MedDRA basket
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count
[3] Table presents number and percentage of patients (n (%)) and number of events (E)
[4] Percentages are based on the number of patients in the respective group
[5] Only one event is counted for multiple occurrences of the same AE (preferred term) in a patient

Table 14.3.5.9.10.1b Administration Related Reactions by System Organ Class and Preferred Term - Whole Study, Reduced Event Count (Safety Population)

System Organ Class Preferred Term	Cohort A (N=1864) n (%)	E	Cohort B (N=709) n (%)	E	Overall (N=2573) n (%)	E
Cardiac Disorders	3 (0.2)	3	0	0	3 (0.1)	3
Cyanosis	2 (0.1)	2	0	0	2 (0.1)	2
Cardio-Respiratory Arrest	1 (0.1)	1	0	0	1 (0.0)	1
Investigations	0	0	1 (0.1)	1	1 (0.0)	1
Blood Pressure Decreased	0	0	1 (0.1)	1	1 (0.0)	1

Roche: M028048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/AECRI2XP.SAS
Produced: 19 February 2016, 11:43
Source: Listing 16.2.7.8
Notes: [1] Administration Related Reaction is defined as all events based on a MedDRA basket
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count
[3] Table presents number and percentage of patients (n (%)) and number of events (E)
[4] Percentages are based on the number of patients in the respective group
[5] Only one event is counted for multiple occurrences of the same AE (preferred term) in a patient

Table 22 Administration-Related Reactions, Severity & Frequency: BO22227 - IV ARM

stae17irr_se Summary of CTC Grading (Worst Case) for Administration-Related Reactions (MedDRA basket) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB IV; N = 298

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	111 (37.2)	94 (31.5)	34 (11.4)	6 (2.0)	-	-
Total Number of AEs	200	150	44	6	-	-
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Total Pts With at Least one AE	67 (22.5)	57 (19.1)	16 (5.4)	-	-	-
RASH	44 (14.8)	31 (10.4)	13 (4.4)	-	-	-
PRURITUS	27 (9.1)	25 (8.4)	2 (0.7)	-	-	-
ERYTHEMA	8 (2.7)	7 (2.3)	1 (0.3)	-	-	-
URTICARIA	2 (0.7)	2 (0.7)	-	-	-	-
PRURITUS GENERALISED	1 (0.3)	1 (0.3)	-	-	-	-
RASH GENERALISED	1 (0.3)	-	1 (0.3)	-	-	-
Total Number of AEs	83	66	17	-	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Total Pts With at Least one AE	41 (13.8)	32 (10.7)	9 (3.0)	-	-	-
COUGH	24 (8.1)	20 (6.7)	4 (1.3)	-	-	-
DYSPNOEA	22 (7.4)	18 (6.0)	4 (1.3)	-	-	-
BRONCHOSPASM	1 (0.3)	-	1 (0.3)	-	-	-
Total Number of AEs	47	38	9	-	-	-
IMMUNE SYSTEM DISORDERS						
Total Pts With at Least one AE	22 (7.4)	10 (3.4)	9 (3.0)	4 (1.3)	-	-
HYPERSENSITIVITY	14 (4.7)	7 (2.3)	4 (1.3)	3 (1.0)	-	-
DRUG HYPERSENSITIVITY	9 (3.0)	3 (1.0)	5 (1.7)	1 (0.3)	-	-
Total Number of AEs	23	10	9	4	-	-

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
Only includes events occurring during treatment phase
AE17 03MAY2017:22:30:47 (1 of 4)

stae17irr_se Summary of CTC Grading (Worst Case) for Administration-Related Reactions (MedDRA basket) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB IV; N = 298

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Total Pts With at Least one AE	19 (6.4)	16 (5.4)	3 (1.0)	-	-	-
OEDEMA	15 (5.0)	12 (4.0)	3 (1.0)	-	-	-
CHEST DISCOMFORT	6 (2.0)	6 (2.0)	-	-	-	-
FACE OEDEMA	1 (0.3)	1 (0.3)	-	-	-	-
SWELLING	1 (0.3)	1 (0.3)	-	-	-	-
Total Number of AEs	23	20	3	-	-	-
VASCULAR DISORDERS						
Total Pts With at Least one AE	17 (5.7)	11 (3.7)	4 (1.3)	2 (0.7)	-	-
FLUSHING	12 (4.0)	10 (3.4)	2 (0.7)	-	-	-
HYPOTENSION	5 (1.7)	1 (0.3)	2 (0.7)	2 (0.7)	-	-
Total Number of AEs	17	11	4	2	-	-
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
Total Pts With at Least one AE	5 (1.7)	3 (1.0)	2 (0.7)	-	-	-
INFUSION RELATED REACTION	5 (1.7)	3 (1.0)	2 (0.7)	-	-	-
Total Number of AEs	5	3	2	-	-	-
EYE DISORDERS						
Total Pts With at Least one AE	2 (0.7)	2 (0.7)	-	-	-	-
EYE PRURITUS	2 (0.7)	2 (0.7)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
Only includes events occurring during treatment phase
AE17 03MAY2017:22:30:47 (2 of 4)

Table 23 Administration-Related Reactions, Severity & Frequency: BO22227 - SC ARM

stae17irr_se Summary of CTC Grading (Worst Case) for Administration-Related Reactions (MedDRA basket) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB SC; N = 297

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	142 (47.8)	121 (40.7)	50 (16.8)	5 (1.7)	-	-
Total Number of AEs	234	168	61	5	-	-
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Total Pts With at Least one AE	90 (30.3)	68 (22.9)	24 (8.1)	1 (0.3)	-	-
RASH	48 (16.2)	37 (12.5)	11 (3.7)	-	-	-
PRURITUS	26 (8.8)	19 (6.4)	7 (2.4)	-	-	-
ERYTHEMA	21 (7.1)	16 (5.4)	4 (1.3)	1 (0.3)	-	-
RASH PRURITIC	3 (1.0)	2 (0.7)	1 (0.3)	-	-	-
URTICARIA	2 (0.7)	2 (0.7)	-	-	-	-
RASH ERYTHEMATOUS	1 (0.3)	-	1 (0.3)	-	-	-
RASH GENERALISED	1 (0.3)	-	1 (0.3)	-	-	-
SWELLING FACE	1 (0.3)	1 (0.3)	-	-	-	-
Total Number of AEs	103	77	25	1	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Total Pts With at Least one AE	52 (17.5)	39 (13.1)	16 (5.4)	1 (0.3)	-	-
COUGH	35 (11.8)	29 (9.8)	5 (1.7)	1 (0.3)	-	-
DYSPNOEA	21 (7.1)	13 (4.4)	8 (2.7)	-	-	-
ASTHMA	1 (0.3)	-	1 (0.3)	-	-	-
HYPERVENTILATION	1 (0.3)	-	1 (0.3)	-	-	-
LARYNGEAL OEDEMA	1 (0.3)	-	1 (0.3)	-	-	-
Total Number of AEs	59	42	16	1	-	-
IMMUNE SYSTEM DISORDERS						
Total Pts With at Least one AE	20 (6.7)	9 (3.0)	8 (2.7)	3 (1.0)	-	-
DRUG HYPERSENSITIVITY	11 (3.7)	6 (2.0)	3 (1.0)	2 (0.7)	-	-
HYPERSENSITIVITY	9 (3.0)	3 (1.0)	5 (1.7)	1 (0.3)	-	-
Total Number of AEs	20	9	8	3	-	-

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
Only includes events occurring during treatment phase
AE17 03MAY2017:22:30:47 (3 of 4)

stae17irr_se Summary of CTC Grading (Worst Case) for Administration-Related Reactions (MedDRA basket) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB SC; N = 297

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS												
Total Pts With at Least one AE	18	(6.1)	17	(5.7)	1	(0.3)	-		-		-	
OEDEMA	10	(3.4)	9	(3.0)	1	(0.3)	-		-		-	
CHEST DISCOMFORT	8	(2.7)	7	(2.4)	1	(0.3)	-		-		-	
FACE OEDEMA	4	(1.3)	4	(1.3)	-		-		-		-	
SWELLING	1	(0.3)	1	(0.3)	-		-		-		-	
Total Number of AEs	23		21		2		-		-		-	
VASCULAR DISORDERS												
Total Pts With at Least one AE	18	(6.1)	15	(5.1)	3	(1.0)	-		-		-	
FLUSHING	13	(4.4)	11	(3.7)	2	(0.7)	-		-		-	
HYPOTENSION	5	(1.7)	4	(1.3)	1	(0.3)	-		-		-	
Total Number of AEs	18		15		3		-		-		-	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS												
Total Pts With at Least one AE	7	(2.4)	2	(0.7)	5	(1.7)	-		-		-	
INFUSION RELATED REACTION	7	(2.4)	2	(0.7)	5	(1.7)	-		-		-	
Total Number of AEs	7		2		5		-		-		-	
EYE DISORDERS												
Total Pts With at Least one AE	4	(1.3)	2	(0.7)	2	(0.7)	-		-		-	
EYE PRURITUS	3	(1.0)	2	(0.7)	1	(0.3)	-		-		-	
PERIORBITAL OEDEMA	1	(0.3)	-		1	(0.3)	-		-		-	
Total Number of AEs	4		2		2		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
Only includes events occurring during treatment phase
AE17 03MAY2017:22:30:47 (4 of 4)

Table 24 Administration-Related Reactions, Overview: MO22982

Cohort 1 and 2 System Organ Class Preferred Term	SC Period (N=479) n	(%)	E	IV Period (N=478) n	(%)	E
Number of Administration Related Adverse Events	61	(12.7)	90	31	(6.5)	38
Skin And Subcutaneous Tissue Disorders	32	(6.7)	45	16	(3.3)	19
Erythema	17	(3.5)	23	6	(1.3)	6
Rash	8	(1.7)	10	6	(1.3)	8
Pruritus	4	(0.8)	4	3	(0.6)	3
Urticaria	1	(0.2)	1	0		
Pruritus Generalised	2	(0.4)	2	0		
Generalised Erythema	1	(0.2)	1	0		
Rash Generalised	0			0		
Rash Pruritic	1	(0.2)	4	1	(0.2)	2
Respiratory, Thoracic And Mediastinal Disorders	18	(3.8)	21	12	(2.5)	13
Cough	9	(1.9)	9	6	(1.3)	6
Dyspnoea	9	(1.9)	12	5	(1.0)	6
Wheezing	0			1	(0.2)	1
Vascular Disorders	8	(1.7)	18	1	(0.2)	1
Flushing	7	(1.5)	17	1	(0.2)	1
Hypotension	1	(0.2)	1	0		

Cohort 1 and 2

System Organ Class Preferred Term	SC Period (N=479) n	(%)	E	IV Period (N=478) n	(%)	E
General Disorders And Administration Site Conditions	4	(0.8)	5	1	(0.2)	1
Chest Discomfort	2	(0.4)	2	1	(0.2)	1
Oedema	2	(0.4)	3	0		
Immune System Disorders	0			4	(0.8)	4
Drug Hypersensitivity	0			3	(0.6)	3
Hypersensitivity	0			1	(0.2)	1
Gastrointestinal Disorders	1	(0.2)	1	0		
Lip Swelling	1	(0.2)	1	0		

Roche: MO22982/CIL-TS/FINAL/AEC01P.SAS
Produced: 16 March 2016, 11:26
Source: Listing 16.2.7.8

Notes: [1] All administration related Adverse Events including Serious Adverse Events are included in summary statistics.
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
[3] If an AE start date is partially or fully missing, and it is unclear during to which treatment period the AE started, the AE has been assigned to all relevant treatment periods.
[4] Table presents number and percentage of patients (n (%)) and number of events (E).
[5] Percentages are based on the number of patients in the respective group.

Table 25 Administration-Related Reactions, Severity & Frequency: MO22982

Cohort 1 and 2 CTC grade System Organ Class Preferred Term	SC Period (N=479) n (%)	E	IV Period (N=478) n (%)	E
Severe				
Number of Administration Related Adverse Events	5 (1.0)	5	2 (0.4)	2
Skin And Subcutaneous Tissue Disorders	4 (0.8)	4	1 (0.2)	1
Erythema	1 (0.2)	1	0	
Generalised Erythema	1 (0.2)	1	0	
Pruritus	1 (0.2)	1	0	
Pruritus Generalised	1 (0.2)	1	0	
Rash Pruritic	0		1 (0.2)	1
Respiratory, Thoracic And Mediastinal Disorders	1 (0.2)	1	1 (0.2)	1
Dyspnoea	1 (0.2)	1	1 (0.2)	1

Cohort 1 and 2 CTC grade System Organ Class Preferred Term	SC Period (N=479) n (%)	E	IV Period (N=478) n (%)	E
Moderate				
Number of Administration Related Adverse Events	14 (2.9)	19	11 (2.3)	11
Skin And Subcutaneous Tissue Disorders	9 (1.9)	13	5 (1.0)	5
Erythema	4 (0.8)	4	3 (0.6)	3
Rash	3 (0.6)	3	1 (0.2)	1
Pruritus	2 (0.4)	2	0	
Rash Pruritic	1 (0.2)	4	1 (0.2)	1
Urticaria	0		0	
Respiratory, Thoracic And Mediastinal Disorders	4 (0.8)	4	3 (0.6)	3
Cough	2 (0.4)	2	1 (0.2)	1
Dyspnoea	2 (0.4)	2	2 (0.4)	2
Immune System Disorders	0		2 (0.4)	2
Drug Hypersensitivity	0		2 (0.4)	2
Hypersensitivity	0		0	

Cohort 1 and 2 CTC grade System Organ Class Preferred Term	SC Period (N=479) n (%)	E	IV Period (N=478) n (%)	E
Moderate				
Vascular Disorders	1 (0.2)	1	1 (0.2)	1
Flushing	1 (0.2)	1	1 (0.2)	1
Hypotension	0		0	
General Disorders And Administration Site Conditions	1 (0.2)	1	0	
Chest Discomfort	1 (0.2)	1	0	

Cohort 1 and 2 CTC grade System Organ Class Preferred Term	SC Period (N=479) n	(%)	E	IV Period (N=478) n	(%)	E
Mild						
Number of Administration Related Adverse Events	45	(9.4)	66	20	(4.2)	25
Skin And Subcutaneous Tissue Disorders	21	(4.4)	28	11	(2.3)	13
Erythema	12	(2.5)	18	3	(0.6)	3
Rash	6	(1.3)	7	5	(1.0)	7
Pruritus	1	(0.2)	1	3	(0.6)	3
Urticaria	1	(0.2)	1	0		
Pruritus Generalised	1	(0.2)	1	0		
Rash Generalised	0			0		
Respiratory, Thoracic And Mediastinal Disorders	14	(2.9)	16	8	(1.7)	9
Cough	7	(1.5)	7	5	(1.0)	5
Dyspnoea	7	(1.5)	9	2	(0.4)	3
Wheezing	0			1	(0.2)	1
Vascular Disorders	7	(1.5)	17	0		
Flushing	6	(1.3)	16	0		
Hypotension	1	(0.2)	1	0		

Cohort 1 and 2 CTC grade System Organ Class Preferred Term	SC Period (N=479) n (%)	E	IV Period (N=478) n (%)	E
Mild				
General Disorders And Administration Site Conditions	3 (0.6)	4	1 (0.2)	1
Chest Discomfort	1 (0.2)	1	1 (0.2)	1
Oedema	2 (0.4)	3	0	
Immune System Disorders	0		2 (0.4)	2
Hypersensitivity	0		1 (0.2)	1
Drug Hypersensitivity	0		1 (0.2)	1
Gastrointestinal Disorders	1 (0.2)	1	0	
Lip Swelling	1 (0.2)	1	0	

Notes: [1] All administration related Adverse Events including Serious Adverse Events are included in summary statistics.
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
[3] If an AE start date is partially or fully missing, and it is unclear during to which treatment period the AE started, the AE has been assigned to all relevant treatment periods.
[4] Table presents number and percentage of patients (n (%)) and number of events (E).
[5] Percentages are based on the number of patients in the respective group.

Table 26 Administration-Related Reactions, Global Safety Database: Summary Tabulation of Adverse Events by SOC

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
System Organ Class	**Preferred Term**					
Immune system disorders	Anaphylactic reaction	201	203	3.8	203	1.2
	Anaphylactic shock	99	100	1.9	100	0.6
	Anaphylactoid reaction	29	29	0.5	29	0.2
	Anaphylactoid shock	2	2	0.0	2	0.0
	Drug hypersensitivity	145	81	1.5	150	0.9
	Hypersensitivity	1016	506	9.5	1034	6.2
	Type I hypersensitivity	1	1	0.0	1	0.0
Eye disorders	Eye oedema	9	2	0.0	9	0.1
	Eye pruritus	33	5	0.1	33	0.2
	Eye swelling	38	6	0.1	39	0.2
	Eyelid oedema	28	8	0.2	28	0.2
	Ocular hyperaemia	50	10	0.2	51	0.3
	Periorbital oedema	10	2	0.0	10	0.1
	Periorbital swelling	11	0	0.0	11	0.1
	Swelling of eyelid	14	3	0.1	14	0.1
Cardiac disorders	Cardiac arrest	112	110	2.1	113	0.7
	Cardio-respiratory arrest	47	46	0.9	47	0.3
	Cardio-respiratory distress	1	1	0.0	1	0.0
	Cardiovascular insufficiency	12	9	0.2	12	0.1
	Cyanosis	64	35	0.7	65	0.4

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
Vascular disorders	Circulatory collapse	57	53	1.0	57	0.3
	Flushing	255	50	0.9	260	1.6
	Hypotension	529	285	5.4	536	3.2
	Shock	39	38	0.7	40	0.2
	Shock symptom	3	3	0.1	3	0.0
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	30	30	0.6	30	0.2
	Asthma	123	62	1.2	123	0.7
	Bronchospasm	114	93	1.7	116	0.7
	Choking	8	4	0.1	8	0.0
	Choking sensation	15	5	0.1	15	0.1
	Cough	1373	164	3.1	1403	8.4
	Dyspnoea	2893	1348	25.4	2952	17.7
	Hyperventilation	8	4	0.1	8	0.0
	Irregular breathing	10	0	0.0	10	0.1
	Laryngeal oedema	18	15	0.3	18	0.1
	Laryngospasm	6	2	0.0	6	0.0
	Nasal obstruction	12	2	0.0	12	0.1
	Oropharyngeal swelling	1	0	0.0	1	0.0
	Pharyngeal oedema	6	3	0.1	6	0.0
	Pharyngeal swelling	16	6	0.1	16	0.1
	Respiratory arrest	32	29	0.5	32	0.2
	Respiratory distress	99	87	1.6	99	0.6
	Respiratory failure	222	218	4.1	226	1.4
	Sneezing	46	0	0.0	46	0.3

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
	Stridor	8	3	0.1	8	0.0
	Tachypnoea	31	17	0.3	31	0.2
	Throat tightness	41	13	0.2	41	0.2
	Upper airway obstruction	1	1	0.0	1	0.0
	Wheezing	87	25	0.5	87	0.5
Gastrointestinal disorders	Lip oedema	6	3	0.1	6	0.0
	Lip swelling	14	3	0.1	14	0.1
	Mouth swelling	10	2	0.0	10	0.1
	Oedema mouth	4	2	0.0	4	0.0
	Swollen tongue	19	5	0.1	19	0.1
	Tongue oedema	5	2	0.0	5	0.0
Skin and subcutaneous tissue disorders	Angioedema	58	45	0.8	58	0.3
	Circumoral oedema	1	1	0.0	1	0.0
	Circumoral swelling	1	0	0.0	1	0.0
	Erythema	912	129	2.4	955	5.7
	Nodular rash	1	0	0.0	1	0.0
	Pruritus	1169	110	2.1	1199	7.2
	Pruritus allergic	2	0	0.0	2	0.0
	Rash	2582	335	6.3	2642	15.9
	Rash erythematous	117	19	0.4	117	0.7
	Rash pruritic	111	13	0.2	114	0.7
	Skin swelling	4	1	0.0	4	0.0
	Urticaria	329	75	1.4	334	2.0

Table 27 Administration-Related Reactions, Global Safety Database: Summary Tabulation Adverse Event by Outcome

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/ Resolved	Recovered/ Resolved With Sequelae	Recovering/ Resolving	Unknown	
Acute respiratory failure	0	12	0	4	1	6	0	4	3	30
Anaphylactic reaction	0	6	0	2	43	101	1	21	29	203
Anaphylactic shock	0	6	0	2	13	70	1	6	2	100
Anaphylactoid reaction	0	0	0	1	1	18	0	6	3	29
Anaphylactoid shock	0	0	0	0	0	2	0	0	0	2
Angioedema	1	3	1	3	7	25	1	6	11	58
Asthma	0	3	0	21	28	31	2	16	22	123
Blood pressure decreased	0	1	0	8	35	63	0	14	25	146
Blood pressure diastolic decreased	0	0	0	0	7	2	0	0	15	24
Blood pressure systolic decreased	0	0	0	0	1	3	0	1	6	11
Bronchospasm	4	5	1	3	19	63	1	13	7	116
Cardiac arrest	1	63	1	2	12	21	6	1	6	113
Cardio-respiratory arrest	1	35	0	1	0	8	0	1	1	47
Cardio-respiratory distress	0	0	0	0	0	0	0	1	0	1
Cardiovascular insufficiency	0	2	0	2	2	4	1	0	1	12
Chest discomfort	5	1	12	46	150	130	2	47	32	425
Choking	0	0	0	1	4	1	0	1	1	8
Choking sensation	0	0	0	2	6	5	0	1	1	15
Circulatory collapse	3	8	0	1	18	20	1	2	4	57
Circumoral oedema	0	0	0	0	0	1	0	0	0	1
Circumoral swelling	0	0	0	0	0	1	0	0	0	1
Cough	14	5	13	296	553	253	3	128	138	1403

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/ Resolved	Recovered/ Resolved With Sequelae	Recovering/ Resolving	Unknown	
Cyanosis	9	1	0	5	4	36	2	5	3	65
Drug hypersensitivity	0	0	0	6	50	73	0	5	16	150
Dyspnoea	81	63	64	453	878	758	32	317	306	2952
Erythema	5	0	16	151	303	297	3	106	74	955
Eye oedema	0	0	0	4	2	3	0	0	0	9
Eye pruritus	0	0	0	8	12	7	0	3	3	33
Eye swelling	0	0	0	9	13	9	0	3	5	39
Eyelid oedema	0	0	0	2	9	10	0	4	3	28
Face oedema	0	0	0	18	20	32	1	13	13	97
Flushing	3	0	7	27	76	96	2	25	24	260
Hypersensitivity	0	3	11	67	283	464	3	55	148	1034
Hyperventilation	0	0	0	1	1	6	0	0	0	8
Hypotension	14	9	10	49	121	213	0	37	83	536
Infusion related reaction	0	6	15	19	232	782	4	109	257	1424
Injection site hypersensitivity	0	0	0	0	4	1	0	0	0	5
Injection site urticaria	0	0	0	1	1	7	0	0	0	9
Irregular breathing	0	0	0	0	10	0	0	0	0	10
Laryngeal oedema	1	0	0	1	1	12	0	2	1	18
Laryngospasm	0	0	0	0	1	4	1	0	0	6
Lip oedema	0	0	0	1	0	2	0	3	0	6
Lip swelling	1	0	0	2	3	5	0	1	2	14
Mouth swelling	0	0	0	4	4	1	0	0	1	10
Nasal obstruction	0	0	0	4	3	4	0	0	1	12
Nodular rash	0	0	0	0	0	1	0	0	0	1

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/ Resolved	Recovered/ Resolved With Sequelae	Recovering/ Resolving	Unknown	
Ocular hyperaemia	2	0	0	10	19	12	0	2	6	51
Oedema	1	2	2	105	134	110	1	61	57	473
Oedema mouth	0	0	0	2	0	2	0	0	0	4
Oropharyngeal swelling	0	0	0	0	1	0	0	0	0	1
Periorbital oedema	1	0	0	0	3	3	0	0	3	10
Periorbital swelling	0	0	0	1	6	1	0	0	3	11
Pharyngeal oedema	0	0	0	2	1	1	0	0	2	6
Pharyngeal swelling	0	0	1	2	2	7	0	2	2	16
Pruritus	4	0	16	318	373	269	4	108	107	1199
Pruritus allergic	0	0	0	0	1	1	0	0	0	2
Rash	2	2	22	455	851	647	8	333	322	2642
Rash erythematous	0	0	1	23	48	22	0	12	11	117
Rash pruritic	0	0	3	29	45	20	0	12	5	114
Respiratory arrest	2	16	2	1	5	5	0	0	1	32
Respiratory distress	5	20	1	5	13	26	0	18	11	99
Respiratory failure	5	110	1	19	20	36	1	24	10	226
Sensation of foreign body	0	0	1	1	4	1	0	0	1	8
Shock	1	8	0	5	7	11	1	3	4	40
Shock symptom	0	0	0	0	0	1	0	1	1	3
Skin swelling	0	0	0	2	0	1	0	0	1	4
Sneezing	0	0	0	3	19	16	0	2	6	46
Stridor	1	0	0	1	1	3	0	1	1	8
Swelling	2	0	5	77	113	36	0	24	32	289
Swelling face	1	0	4	22	32	26	0	17	11	113

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/ Resolved	Recovered/ Resolved With Sequelae	Recovering/ Resolving	Unknown	
Swelling of eyelid	0	0	1	2	6	1	0	3	1	14
Swollen tongue	0	0	3	4	5	6	0	0	1	19
Tachypnoea	1	1	0	6	7	12	0	2	2	31
Throat tightness	1	0	1	2	11	14	2	4	6	41
Tongue oedema	0	0	0	1	1	2	1	0	0	5
Tracheal obstruction	0	0	0	0	0	0	0	1	0	1
Type I hypersensitivity	0	0	0	0	0	1	0	0	0	1
Upper airway obstruction	0	0	0	1	0	0	0	0	0	1
Urticaria	3	0	10	48	69	109	3	41	51	334
Wheezing	6	0	3	4	34	21	0	8	11	87
Total	**181**	**391**	**228**	**2378**	**4762**	**5074**	**88**	**1636**	**1916**	**16654**

Data cutoff: 24 September 2018. Exposure cut-off: 24 September 2018. Comanifestations are counted as AE

Table 28 Administration-Related Reactions, Global Safety Database: Summary Tabulation Event Outcome by Action Taken

Outcome	Blank	Coman	Dose Increased	Dose Interrupted	Dose Modified NOS	Dose Not Changed	Dose Reduced	Drug Withdrawn	Infusion Rate Decreased	Not Applicable	Unknown	Total No. Drug Events
Coman	0	181	0	0	0	0	0	0	0	0	0	181
Fatal	0	0	0	4	0	19	1	46	0	247	74	391
Not Applicable	0	0	0	0	0	0	0	1	0	224	4	229
Not Recovered/Not Resolved	2	0	2	64	1	878	13	276	0	197	975	2408
Not Reported	0	0	3	127	1	334	11	280	3	114	3951	4824
Recovered/Resolved	1	0	4	423	7	1437	27	1211	14	303	1699	5126
Recovered/Resolved With Sequelae	0	0	0	6	0	25	0	27	0	4	26	88
Recovering/Resolving	1	0	1	78	1	448	7	395	4	112	599	1646
Unknown	0	0	0	46	3	300	3	285	0	217	1070	1924

Data cutoff: 24 September 2018. Exposure cut-off: 24 September 2018. Comanifestations are counted as AE

3. OLIGOHYDRAMNIOS

Table 29 Oligohydramnios, Global Safety Database: Summary Tabulation of Adverse Events by SOC

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
System Organ Class	**Preferred Term**					
Infections and infestations	Omphalitis	1	0	0.0	1	1.0
Blood and lymphatic system disorders	Thrombocytopenia neonatal	1	1	1.2	1	1.0
Metabolism and nutrition disorders	Failure to thrive	11	10	12.0	11	10.6
Nervous system disorders	Agitation neonatal	1	1	1.2	1	1.0
Respiratory, thoracic and mediastinal disorders	Meconium aspiration syndrome	1	1	1.2	1	1.0
	Neonatal anoxia	1	1	1.2	1	1.0
	Neonatal respiratory distress syndrome	5	5	6.0	5	4.8
	Transient tachypnoea of the newborn	2	2	2.4	2	1.9
Pregnancy, puerperium and perinatal conditions	Jaundice neonatal	1	0	0.0	1	1.0
	Low birth weight baby	1	0	0.0	1	1.0
	Neonatal disorder	1	1	1.2	1	1.0
	Oligohydramnios	46	41	49.4	47	45.2
	Polyhydramnios	4	4	4.8	4	3.8
	Premature baby	12	8	9.6	12	11.5
	Small for dates baby	5	1	1.2	5	4.8
	Umbilical cord abnormality	2	1	1.2	2	1.9
General disorders and administration site conditions	Death neonatal	2	2	2.4	2	1.9
Investigations	Amniotic fluid volume decreased	6	4	4.8	6	5.8
Total		**N/A**	**83**	**100.0**	**104**	**100.0**

Table 30 Oligohydramnios, Global Safety Database: Summary Tabulation Adverse Event by Outcome

	Event outcome									
Preferred Term	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/ Resolved	Recovered/ Resolved With Sequelae	Recovering/ Resolving	Unknown	Total No. AEs
Agitation neonatal	0	0	0	0	0	1	0	0	0	1
Amniotic fluid volume decreased	0	0	0	1	1	4	0	0	0	6
Death neonatal	0	1	1	0	0	0	0	0	0	2
Failure to thrive	1	1	0	1	1	5	1	0	1	11
Jaundice neonatal	0	0	0	0	1	0	0	0	0	1
Low birth weight baby	0	0	1	0	0	0	0	0	0	1
Meconium aspiration syndrome	0	0	0	0	0	1	0	0	0	1
Neonatal anoxia	0	0	0	1	0	0	0	0	0	1
Neonatal disorder	0	0	0	0	0	1	0	0	0	1
Neonatal respiratory distress syndrome	0	0	0	0	1	2	0	0	2	5
Oligohydramnios	0	0	5	3	13	13	0	0	13	47
Omphalitis	0	0	0	0	1	0	0	0	0	1
Polyhydramnios	0	0	0	0	2	2	0	0	0	4
Premature baby	0	2	8	0	0	0	0	1	1	12
Small for dates baby	0	0	0	0	2	3	0	0	0	5
Thrombocytopenia neonatal	0	0	0	0	0	1	0	0	0	1
Transient tachypnoea of the newborn	0	0	0	0	0	1	0	0	1	2
Umbilical cord abnormality	0	1	1	0	0	0	0	0	0	2
Total	**1**	**5**	**16**	**6**	**22**	**34**	**1**	**1**	**18**	**104**

Table 31 Oligohydramnios, Global Safety Database: Summary Tabulation of Event Outcome by Action Taken

	Coman	Dose Interrupted	Dose Not Changed	Drug Withdrawn	Not Applicable	Unknown	Total No. Drug Events
Coman	1	0	0	0	0	0	1
Fatal	0	0	0	0	4	1	5
Not Applicable	0	0	0	1	15	0	16
Not Recovered/Not Resolved	0	0	1	4	1	0	6
Not Reported	0	1	0	6	4	11	22
Recovered/Resolved	0	5	3	10	9	7	34
Recovered/Resolved With Sequelae	0	0	0	0	0	1	1
Recovering/Resolving	0	0	0	0	0	1	1
Unknown	0	0	0	3	8	7	18
Total	**1**	**6**	**4**	**24**	**41**	**28**	**104**

4. IMMUNOGENICITY/ HYPERSENSITIVITY AND ANAPHYLAXIS OF HERCEPTIN SC

Table 32 Brighton collaboration criteria terms: BO22227

Pt.#	AE: preferred term	Treated?	Outcome of AE	CTC grade	Phase of treatment	Trastuzumab cycle
[redacted]	Tachycardia	Yes	Resolved	1	Neoadjuvant	5
	Tachycardia	No	Resolved	1	Neoadjuvant	5
	Tachycardia	No	Resolved	1	Neoadjuvant	3
	Tachycardia	Yes	Resolved	1	Adjuvant	17
	Tachycardia	No	Persisting	1	Follow-up	N/A
	Hypotension	No	Resolved	2	Neoadjuvant	4
	Hypotension	No	Resolved	1	Neoadjuvant	7
	Hypotension	No	Persisting	1	Adjuvant	18
	Hypotension	Yes	Resolved	2	Adjuvant	9
	Laryngeal oedema	No	Resolved	2	Neoadjuvant	4
	Rash generalised	No	Resolved	2	Adjuvant	11

Table 33 Summary of Anti-Trastuzumab Antibodies (SP): BO22227

		Herceptin IV N = 298	Herceptin SC N = 297
Number of patients with ADA results		298	297
	BL with no post-BL	2	2
Number of patients evaluable for ADA to trastuzumab		296	295
Evaluation of ADA			
	response BL→post-BL		
Positive Response			
	positive→positive	5	7
	NAb positive	2[a]	3[b]
	negative→positive	28	46
	NAb positive	1	3
	no sample→positive	0	0
	NAb positive	0	0
ADA Incidence (%) [c]		11.1% (33/296)	18.0% (53/295)

ADA = anti-drug antibody; BL = baseline; IV = intravenous; NAb = neutralizing antibody; SC = subcutaneous; SP = safety analysis population.

[a] One patient tested NAb positive at baseline only.

[b] Two patients tested NAb positive at baseline only.

[c] ADA incidence (%) is the cumulative number of post-baseline antibody positive patients of the treatment and treatment-free follow-up phases combined, irrespective of response at BL.

Source: etabsum_SAF_ABTRASetabsum_SAF_ABTRAS; elata_SAFelata_SAF

Table 34 Summary of the Incidence of Anti-Trastuzumab Antibodies (SP) (New Definition)

	Herceptin IV N = 298	Herceptin SC N = 297
Number of patients with ADA results	298	297
BL with no post-BL	2	2
Number of patients evaluable for ADA to trastuzumab	296	295
Evaluation of ADA		
Treatment- induced ADA	28	46
NAb positive	1	3
Treatment-enhanced ADA	2	1
NAb positive	2 [a]	0
Treatment-unaffected ADA	16	15
NAb positive	3 [b]	4 [b]
ADA Incidence (%) [c]	10.1% (30/296)	15.9% (47/295)

ADA = anti-drug antibody; BL = baseline; IV = intravenous; NAb = neutralizing antibody; SC = subcutaneous; SP = safety analysis population.

[a] One patient tested NAb positive at baseline only.

[b] Three patients tested NAb positive at baseline only.

[c] Incidence of ADA (%) is the cumulative treatment-induced and treatment-enhanced ADA of the treatment and treatment-free follow-up phases combined.

Treatment-induced ADA = a patient with negative or missing BL ADA results and at least one positive post-BL ADA result.

Treatment -enhanced ADA = a patient with positive ADA result at BL who has one or more post-BL titer results that are at least 0.60 titer units greater than the BL titer result (four-fold increase of titer).

Treatment-unaffected ADA = a post-baseline evaluable patient with a positive ADA result at BL and (a) where all post-BL titer results are less than 0.60 titer units greater than the BL titer result (no 4-fold increase of titer), or (b) where all post-BL results are negative, irrespective of the response at BL.

Source: etabsum2_SAF_ABTRASetabsum2_SAF_ABTRAS; elata_SAFelata_SAF

Table 35 Summary of Anti-rHuPH20 Antibodies (SP): BO22227

	Herceptin SC
	N=297
Number of patients with ADA results	297
BL with no post-BL	2
Number of patients evaluable for ADA to trastuzumab	295
Evaluation of ADA response BL→post-BL	
Positive Response	
positive→positive	21
Nab positive	0
negative→positive	48
Nab positive	0
no sample→positive	1
Nab Positive	0
ADA Rate (%) [a]	23.7% (70/295)

ADA=anti-drug antibody; BL=baseline Nab=Neutralizing Antibody.

[a] ADA rate (%) is the cumulative antibody rate of the treatment and treatment-free follow-up phases combined

Table 36 Summary of Anti-rHuPH20 Antibodies (SP) (New Definition)

		Herceptin SC N = 297
Number of patients with antibody results		297
	BL with no post-BL	2
Number of patients evaluable for antibodies to rHuPH20		295
Evaluation of anti-rHuPH20 Antibodies		
	Treatment-induced	49
	Treatment-enhanced	13
	Treatment-unaffected	9
Incidence of anti-rHuPH20 antibodies (%)[a]		21.0% (62/295)

BL = baseline.

[a] Incidence of anti-rHuPH20 antibodies (%) is the cumulative treatment-induced and treatment-enhanced anti-rHuPH20 antibodies of the treatment and treatment-free follow-up phases combined.

Treatment-induced ADA = a patient with negative or missing BL ADA results and at least one positive post-BL ADA result.

Treatment -enhanced ADA = a patient with positive ADA result at BL who has one or more post-BL titer results that are at least 0.60 titer units greater than the BL titer result (four-fold increase of titer)

Treatment-unaffected ADA = a post-baseline evaluable patient with a positive ADA result at BL and (a) where all post-BL titer results are less than 0.60 titer units greater than the BL titer result (no four-fold increase of titer), or (b) where all post-BL results are negative, irrespective of the response at BL.

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Table 37 Hypersensitivity and Anaphylaxis Observed in SC Patient Population: BO22227

Patient N0	SAE ?	Duration of adverse event	preferred term	Additional treatment given?	Trial medication adjustment	Relation to trial medication	Outcome of adverse event	Chemotherapy adjustment	Phase of treatment	Trastuzumab cycle
Trastuzumab SC										
[redacted]	No	1	Drug hypersensitivity	Yes	None	Yes	Reso- no sequel	Dosage modified	Neo-adjuvant	CYCLE 2
	No	1	Hypersensitivity	Yes	None	Yes	Reso- no sequel	Dosage modified	Neo-adjuvant	CYCLE 2
	No	1	Drug hypersensitivity	Yes	None	Yes	Reso - no sequel	Dosage modified	Neo-adjuvant	CYCLE 2
	No	1	Drug hypersensitivity	Yes	None	Yes	Reso - no sequel	Dosage modified	Neo-adjuvant	CYCLE 3
	No	1	Drug hypersensitivity	Yes	None	Yes	Reso - no sequel	Dosage modified	Neo-adjuvant	CYCLE 4

Table 38 Summary of Anti-Trastuzumab Antibodies (Safety Population; Cohort 1): MO22982

	SC SID/IV N=122			IV/SC SID N=122		
	de Novo	Non de Novo	Overall	de Novo	Non de Novo	Overall
Number of Patients with an trastuzumab ADA result at BL	27	93	120	29	92	121
Evaluation of Trastuzumab immunogenicity at BL						
Number of Patients with trastuzumab ADA-positive results at BL	2	1	3	3	2	5
BL Trastuzumab immunogenicity rate	7.4% (2/27)	1.1% (1/93)	2.5% (3/120)	10.3% (3/29)	2.2% (2/92)	4.1% (5/121)
Number of Patients with at least 1 ADA result	28	94	122	29	93	122
Number of Patients with ADA result at BL only	3	5	8	1	2	3
Number of Patients evaluable for ADA to Trastuzumab	25	89	114	28	91	119
Evaluation of trastuzumab ADAs at BL to Post-BL						
Pos at BL to Pos Post-BL	0	0	0	0	2	2
Neg at BL to Pos Post-BL	0	0	0	1	1	2
No BL to Pos Post-BL	0	0	0	0	0	0
Post-BL Trastuzumab ADA rate	0% (0/25)	0% (0/89)	0% (0/114)	3.6%% (1/28)	3.3% (3/91)	3.4% (4/119)

ADA=anti-drug antibody; BL=Baseline; Neg=negative; Pos=Positive.
Note: Positive is per confirmatory test results.

Table 39 Summary of Anti-rHuPH20 Antibodies (Safety Population; Cohort 1): MO22982

	SC SID/IV n=122			IV/SC SID n=122		
	De Novo	Non de Novo	Overall	De Novo	Non de Novo	Overall
Number of Patients with an rHuPH20 ADA result at BL	27	93	120	29	92	121
Evaluation of rHuPH20 immunogenicity at BL						
Number of patients with rHuPH20 antibody positive results at BL	2	5	7	2	7	9
BL rHuPH20 immunogenicity rate	7.4% (2/27)	5.4% (5/93)	5.8% (7/120)	6.9% (2/29)	7.6% (7/92)	7.4% (9/121)
Number of patients with at least 1 rHuPH20 antibody result	28	94	122	29	93	122
Number of patients with rHuPH20 antibody result at BL only	2	5	7	1	2	3
Number of patients evaluable for antibodies to rHuPH20	26	89	115	28	91	119
Evaluation of rHuPH20 antibody response BL to Post-BL						
Pos at BL to Pos Post-BL	1	2	3	2	5	7
Neg at BL to Pos Post-BL	0	0	0	1	1	2
No BL to Pos Post-BL	0	0	0	0	0	0
Post-BL rHuPH20 antibody rate	3.8% (1/26)	2.2% (2/89)	2.6% (3/115)	10.7% (3/28)	6.6% (6/91)	7.6% (9/119)

Abbreviations: BL=baseline, Neg=negative, Pos=positive

5. SHORT-TERM SAFETY OF HERCEPTIN SC COMPARED TO HERCEPTIN IV

Table 40 Summary of Adverse Events During Crossover Period with or without ISRs: MO22982

Cohort 1 and 2 System Organ Class Preferred Term	SC Period (N=479) n (%)	E	IV Period (N=478) n (%)	E
Number of Adverse Events	300 (62.6)	913	258 (54.0)	581

Excluding ISR

Cohort 1 and 2 System Organ Class Preferred Term	SC Period (N=479) n (%)	E	IV Period (N=478) n (%)	E
Number of Adverse Events	275 (57.4)	727	258 (54.0)	580

Roche: MO22982/CIL-TS/FINAL/AEC01P.SAS
Produced: 16 March 2016, 11:26 Page 32 of 52
Source: Listing 16.2.7.1
Notes: [1] All Adverse Events including Serious Adverse Events are included in summary statistics.
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
[3] If an AE start date is partially or fully missing, and it is unclear during to which treatment period the AE started, the AE has been assigned to all relevant treatment periods.
[4] Table presents number and percentage of patients (n (%)) and number of events (E).
[5] Percentages are based on the number of patients in the respective group.

Table 41 Overview of Serious Adverse Events During Crossover Period: MO22982

Cohort 1 and 2	SC Period (N=479) n	(%)	E	IV Period (N=478) n	(%)	E
Number of SAEs	4	(0.8)	4	4	(0.8)	5
Study Drug Discontinued Due to SAE	0			1	(0.2)	1
Symptomatic Left Ventricular Systolic Dysfunction Events	0			0		
CTC Grade						
Mild	1	(0.2)	1	0		
Moderate	0			1	(0.2)	1
Severe	3	(0.6)	3	4	(0.8)	4
Life Threatening	0			0		
Death	0			0		
Suspected Causal Relationship to Study Medication						
Yes	0			0		
No	4	(0.8)	4	4	(0.8)	5
SAE Outcome						
Resolved/full recovery	4	(0.8)	4	4	(0.8)	5
Resolved with sequelae	0			0		
Ongoing	0			0		
Died	0			0		

Roche: MO22982/CIL-TS/FINAL/AEV01P.SAS
Produced: 16 March 2016, 11:24 Page 6 of 6
Source: Listing 16.2.7.2
Notes: [1] If a patient has multiple events of the same CTC Grade, relationship or outcome, then they are counted only once in that CTC Grade, relationship or outcome. However, patients can be counted more than once overall.
[2] If an AE start date is partially or fully missing, and it is unclear during to which treatment period the AE started, the AE has been assigned to all relevant treatment periods.
[3] Table presents number and percentage of patients (n(%)) and number of events (E).
[4] Percentages are based on the number of patients in the respective group.

Table 42 Summary of Grade 3 or More Adverse Events during the Treatment Period: Safety Population: MO28048

Table 14.3.1.2 Summary of Serious Adverse Events - Treatment Period
(Safety Population)

	Cohort A (N=1864) n	(%)	E	Cohort B (N=709) n	(%)	E	Overall (N=2573) n	(%)	E
Number of SAE	242	(13.0)	316	84	(11.8)	107	326	(12.7)	423
Study Drug Discontinued Due to SAE	24	(1.3)	26	8	(1.1)	8	32	(1.2)	34
Study Drug Interruption Due to SAE	39	(2.1)	46	14	(2.0)	15	53	(2.1)	61
Medical Device Complaint/Events	0			0			0		
Cardiac Adverse Events	31	(1.7)	34	3	(0.4)	3	34	(1.3)	37
CTC Grade									
Mild	19	(1.0)	22	4	(0.6)	4	23	(0.9)	26
Moderate	58	(3.1)	65	21	(3.0)	22	79	(3.1)	87
Severe	157	(8.4)	185	53	(7.5)	65	210	(8.2)	250
Life Threatening	36	(1.9)	41	14	(2.0)	14	50	(1.9)	55
Death	3	(0.2)	3	2	(0.3)	2	5	(0.2)	5
Suspected Causal Relationship to Study Medication									
Yes	35	(1.9)	38	4	(0.6)	4	39	(1.5)	42
No	211	(11.3)	278	82	(11.6)	103	293	(11.4)	381

Roche: MO28048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/AEVOXP.SAS
Produced: 17 August 2015, 5:40 Page 1 of 2
Source: Listing 16.2.7.2
Notes: [1] If a patient has multiple events of the same CTC grade, relationship or outcome, then they are counted only once in that CTC grade relationship or outcome. However, patients can be counted more than once overall
[2] Table presents number and percentage of patients (n (%)) and number of events (E)
[3] Percentages are based on the number of patients in the respective group

Table 14.3.1.2 Summary of Serious Adverse Events - Treatment Period
(Safety Population)

	Cohort A (N=1864) n	(%)	E	Cohort B (N=709) n	(%)	E	Overall (N=2573) n	(%)	E
SAE Outcome									
Resolved/full recovery	228	(12.2)	295	82	(11.6)	103	310	(12.0)	398
Resolved with sequelae	8	(0.4)	9	0			8	(0.3)	9
Ongoing	8	(0.4)	9	2	(0.3)	2	10	(0.4)	11
Died	3	(0.2)	3	2	(0.3)	2	5	(0.2)	5
Was Any Treatment Necessary in Response to SAE?									
Yes	222	(11.9)	283	76	(10.7)	98	298	(11.6)	381
No	32	(1.7)	33	9	(1.3)	9	41	(1.6)	42

Roche: MO28048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/AEVOXP.SAS
Produced: 17 August 2015, 5:40 Page 2 of 2
Source: Listing 16.2.7.2
Notes: [1] If a patient has multiple events of the same CTC grade, relationship or outcome, then they are counted only once in that CTC grade relationship or outcome. However, patients can be counted more than once overall
[2] Table presents number and percentage of patients (n (%)) and number of events (E)
[3] Percentages are based on the number of patients in the respective group

(cont.)

Table 43 Short term safety of Herceptin SC compared to Herceptin IV: Global Safety Database: Summary Tabulation of Adverse Events by SOC

SOC	Trastuzumab (SC)						Trastuzumab (IV)						Trastuzumab (Form Unknown)					
	AEs	%	SAEs	%	Fatal	%	AEs	%	SAEs	%	Fatal	%	AEs	%	SAEs	%	Fatal	%
Blood	156	2.63	83	7.37	0	0.00	1,056	3.67	705	6.52	36	4.47	145	8.49	24	6.30	0	0.00
Card	227	3.83	133	11.81	2	5.71	1,831	6.36	1,415	13.09	81	10.06	63	3.69	41	10.76	3	5.66
Cong	0	0.00	0	0.00	0	0.00	13	0.05	10	0.09	1	0.12	0	0.00	0	0.00	0	0.00
Ear	31	0.52	4	0.36	0	0.00	115	0.40	30	0.28	1	0.12	2	0.12	0	0.00	0	0.00
Endo	12	0.20	1	0.09	0	0.00	32	0.11	23	0.21	0	0.00	3	0.18	1	0.26	0	0.00
Eye	85	1.44	21	1.87	0	0.00	350	1.22	97	0.90	0	0.00	7	0.41	0	0.00	0	0.00
Gastr	616	10.40	78	6.93	1	2.86	3,442	11.96	899	8.32	50	6.21	271	15.87	36	9.45	1	1.89
Genrl	1,172	19.79	150	13.32	18	51.43	4,965	17.25	1,496	13.84	252	31.30	330	19.32	89	23.36	39	73.58
Hepat	15	0.25	8	0.71	0	0.00	217	0.75	121	1.12	20	2.48	8	0.47	5	1.31	0	0.00
Immun	41	0.69	15	1.33	0	0.00	401	1.39	269	2.49	11	1.37	13	0.76	4	1.05	0	0.00
Infec	361	6.09	86	7.64	3	8.57	1,289	4.48	608	5.63	56	6.96	60	3.51	23	6.04	2	3.77
Inj&P	188	3.17	33	2.93	0	0.00	898	3.12	312	2.89	6	0.75	37	2.17	7	1.84	0	0.00
Inv	322	5.44	109	9.68	0	0.00	2,413	8.38	995	9.21	17	2.11	138	8.08	41	10.76	0	0.00
Metab	108	1.82	18	1.60	0	0.00	477	1.66	156	1.44	13	1.61	46	2.69	8	2.10	1	1.89
Musc	705	11.90	69	6.13	0	0.00	1,852	6.44	301	2.78	1	0.12	144	8.43	6	1.57	0	0.00
Neopl	47	0.79	41	3.64	4	11.43	416	1.45	292	2.70	64	7.95	32	1.87	14	3.67	0	0.00
Nerv	482	8.14	70	6.22	0	0.00	2,386	8.29	626	5.79	41	5.09	134	7.85	14	3.67	1	1.89
Preg	2	0.03	1	0.09	0	0.00	17	0.06	10	0.09	0	0.00	1	0.06	1	0.26	0	0.00
Prod	3	0.05	1	0.09	0	0.00	10	0.03	6	0.06	0	0.00	0	0.00	0	0.00	0	0.00

SOC	Trastuzumab (SC)						Trastuzumab (IV)						Trastuzumab (Form Unknown)					
	AEs	%	SAEs	%	Fatal	%	AEs	%	SAEs	%	Fatal	%	AEs	%	SAEs	%	Fatal	%
Psych	133	2.25	16	1.42	0	0.00	455	1.58	87	0.80	5	0.62	18	1.05	3	0.79	0	0.00
Renal	27	0.46	14	1.24	1	2.86	273	0.95	144	1.33	14	1.74	10	0.59	4	1.05	0	0.00
Repro	66	1.11	7	0.62	0	0.00	190	0.66	37	0.34	0	0.00	11	0.64	2	0.52	0	0.00
Resp	333	5.62	84	7.46	6	17.14	2,292	7.96	1,251	11.57	121	15.03	86	5.04	33	8.66	5	9.43
Skin	592	9.99	37	3.29	0	0.00	2,562	8.90	499	4.62	3	0.37	123	7.20	11	2.89	0	0.00
SocCi	1	0.02	0	0.00	0	0.00	12	0.04	3	0.03	0	0.00	0	0.00	0	0.00	0	0.00
Surg	8	0.14	2	0.18	0	0.00	66	0.23	48	0.44	0	0.00	9	0.53	7	1.84	0	0.00
Vasc	190	3.21	45	4.00	0	0.00	748	2.60	368	3.40	12	1.49	17	1.00	7	1.84	1	1.89
Total	**5,923**	**100.00**	**1,126**	**100.00**	**35**	**100.00**	**28,778**	**100.00**	**10,808**	**100.00**	**805**	**100.00**	**1,708**	**100.00**	**381**	**100.00**	**53**	**100.00**

All events from post-marketing source with a latency of ≤1 year from the first dose of Herceptin were compared based on the proportion of AEs, SAEs, and fatal events, reported across the SOCs with a cutoff date of 31 August 2017

Generated using MedDRA Version 19.1.

6. 6. KEY LITERATURE REFERENCED IN THE RMP UPDATE

MRN	Citation
10547	Burstein HJ. Systemic treatment for metastatic breast cancer: General principles. 2019. In: UpToDate [Internet]. Waltham, MA: UpToDate Inc. Available from: https://www.uptodate.com
10534	Hamza A, Herr D, Solomayer EF, et al. Polyhydramnios: causes, diagnosis and therapy. Geburtshilfe Frauenheilkd 2013; 73(12):1241–6.
10537	Myhra W, Davis M, Mueller BA, et al. Maternal smoking and the risk of polyhydramnios. Am J Public Health 1992; 82 (2):176–9.
10538	Oyebode F, Rastogi A, Berrisford G, et al. Psychotropics in pregnancy: safety and other considerations. Pharmacol Ther 2012;135 (1):71–7.
10543	Taghian A et al. Overview of the treatment of newly diagnosed, non-metastatic breast cancer. Available from: https://www.uptodate.com/contents/overview-of-the-treatment-of-newly-diagnosed-non-metastatic-breast-cancer?search=overview-of-the-treatment-of-newly-diagnosed-non-metastatic-breast&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
10444	Yocum RC, Kennard D, Heiner LS. Assessment and implication of the allergic sensitivity to a single dose of recombinant human hyaluronidase injection: a double-blind, placebo-controlled clinical trial. Journal of infusion nursing : the official publication of the Infusion Nurses Society 2007;30:293-9.

ANNEX 8: SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

ANNEX 8: SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval date* Procedure	Change
11.2	26 March 2013	The following were added as new potential risks: Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin subcutaneous (SC) - added as new potential risk. Relative short-term safety of the higher absolute dose intensity of the SC formulation of trastuzumab compared with the intravenous (IV) formulation of trastuzumab- added as new potential risk. “Absolute dose intensity of the SC formulation” was re-named as “Relative long-term safety of the higher absolute dose intensity of the SC formulation of trastuzumab compared with the IV formulation of trastuzumab” as requested in the 180-day assessment report of the SC formulation marketing authorization application (MAA) in the European Economic Area (EEA). Additional information was also included pertaining to the missing information “Safety of 75mg/m^2 v 100mg/m^2 docetaxel dose.”
12.0	19 Nov 2013	Migration into the new EU format and template. Information on the risks is updated as available however the characterization of the risks and the mitigation measures are not changed significantly.
13.0	07 April 2014	Version 13.0 was prepared to support the single-use injection device (SID) filing. No new safety concerns have been added.

Version	Approval date* Procedure	Change
13.1	01 July 2014	Prepared in response to the assessment of v13.0 Potential for medication error involving SID added to Section 7.6
13.2	21 July 2014	Prepared in response to the assessment of v13.1 Updated section 8 added 8.1 and also 16.1 and 16.2
14.0	27 Aug 2014	Prepared to support the submission of the PrefHER data with a label update No new safety concerns have been added. Addition of PrefHER data
15.0	Nov 2014	Annual submission, Prepared also in response to the assessment of the Herceptin Periodic Benefit-Risk Evaluation Report (PBRER) data lock point (DLP) 24 March and the Pharmacovigilance Risk Assessment Committee (PRAC) feedback on the risk management plan (RMP) V.12 and 14 No new safety concerns have been added.
15.1	December 2014	Prepared to support changes to study milestones. No new safety concerns have been added.
15.2	March 2015	Prepared due to Summary of Product Characteristics (SmPC) update and to rectify editorial errors. Submitted with 2y-follow-up data for the BO22227 (HannaH) study No new safety concerns have been added.
16.0	March 2015	Prepared to support the submission of the Study MO28048 (SafeHER) data. No new safety concerns have been added.
16.1	August 2015	Consolidated version prepared by responding to the PRAC Requests for Supplementary Information listed in the Assessment Reports for the Study BO22227 (RMP V 15.2) and the MO28048 (RMP V 16.0) variations. No new safety concerns have been added.
16.2	September 2015	Prepared to support changes to study milestones. No new safety concerns have been added.
16.3	November 2015	Prepared in response to the assessment of version 16.2. Various inconsistencies were removed. No new safety concerns have been added. However, 2 existing safety concerns have been re-named. Immunogenicity information is now presented only for the safety concern of immunogenicity/ Hypersensitivity and Anaphylaxis.

Version	Approval date* Procedure	Change
16.4	28 Feb 2016	Prepared to support change to OHERA milestone
16.5	10 March 2017	Updated to remove information on SID
17.0	April 2017	Updated in response to PRAC assessment questions Exposure from PBRER 1072735 covering the reporting interval 25 September 2015 to 24 September 2016 and medication error and device failure. Updated safety concerns with information from HERA (BO16348), SafeHER (MO28048), PrefHER (MO22982) and global safety database outputs. Updated Annual Data Summary of MotHER. Safety concern of Herceptin SC compared to Herceptin IV updated to add information on immunogenicity. Removed the guided questionnaires (GQs) for infusion related reactions, interstitial lung disease, hemolytic anemia and cardiac adverse events. No new safety concerns have been added.
18.0	28 September 2017	Prepared to support the submission of the Study BO20652 (OHERA) data. Added information on Direct Health Care Professional Communication (DHPC) and post-authorization measure.
19.0	December 2017	Prepared to support the HannaH (BO22227) final data (5-year follow-up data). Revised as per revision 2 of the GVP module V Safety concerns reclassification as per the revised GVP-V definitions of important risks and missing information

Version	Approval date* Procedure	Change
20.0	31 October 2018	Prepared to submit to the European Medicines Agency (EMA) the Annual Data Summaries (ADSs) of the MotHER Registry relating to Herceptin and covering the following time periods: • ADS for the reporting interval of 1 February 2017 through 31 January 2018, presenting annual data (for the reporting interval) and cumulative data from the time of initiation of this registry, 20 December 2008 through the end of the current reporting period 31 January 2018 • ADS for the reporting interval of 1 February 2016 through 31 January 2017, presenting annual data (for the reporting interval) and cumulative data from 20th December 2008 through the end of the reporting period 31 January 2017 In addition, the 2018 ADS (reporting interval of 1 February 2017 through 31 January 2018) is the final report for patients exposed to Herceptin only in the MotHER Registry and is provided in support of the marketing authorization holder's (MAH's) request to close out this RMP commitment of MotHER Registry relating to Herceptin. Updated in response to PRAC assessment comments with respect to E.U. RMP v19.0. Added information on survey results related to the survey to assess compliance with cardiac monitoring label requirements following distribution of DHPC in 2017 (assessed by PRAC under EMEA/H/C/000278/LEG100).
21.0		• Study BO29159 (MetaPHER) has recently been completed. No new information was obtained for the safety concern of cardiac dysfunction and Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin SC. No additional PV activity for the safety concern of cardiac dysfunction and Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin SC were conducted through this trial. Therefore, no

Version	Approval date* Procedure	Change
		further information from this trial will be presented in the future updates to the RMP. The final CSR for this study will be submitted to the EMA with Variation application EMEA/H/C/278/II/XXX, in November 2019 • Cumulative patient exposure data from marketing experience have been updated in line with Periodic Benefit-Risk Evaluation Report) 2018 (Report number 1089226). • Any reference to H4621g/GE28099 (MotHER Pregnancy Registry) has been removed from the RMP as MotHER Registry (H4621g/GE28099) is now closed to all patients exposed to Herceptin, Perjeta (in combination with Herceptin) or Kadcyla. No further additional pharmacovigilance activity will be conducted within the MotHER Registry for the safety concern of oligohydramnios • Additional risk minimization measure of Direct Health Care Professional Communication for increased risk of cardiac dysfunction has been removed as additional risk minimization, hence annex 6 shall be not applicable • Table 27 (Exposure to trial drug following randomization (Cohort 1 and 2, Safety population), Table 40 (Cardiac dysfunction, severity & frequency: BO22227 IV arm), Table 41 (Cardiac dysfunction, severity & frequency: BO22227 SC arm) and Table 42 (Summary of Cardiac events, special population) have been replaced with same outputs with better resolution to increase the legibility. No data for those trials have been updated