EU Risk Management Plan (RMP) for Nerlynx® (neratinib)

RMP version to be assessed as part of this application:

RMP Version number: 2.0

Data lock point for this RMP: 01st May 2020

Date of final sign off: 12th April 2021

Rationale for submitting an updated RMP:

- Update concerning the post authorization safety studies

Summary of significant changes in this RMP:

- Modification of the additional risk minimisation activities concerning the risk diarrhoea:
    - PASS 7402 and PASS 7403 were merged and the new approved protocol of study Nerlyfe - 7402 was added.
    - PASS 6201: New interim report is added and planned date of the final report was delayed.
- The results of the safety pharmacology study on the cardiovascular effects of the metabolite M3 in dogs (Study 20130869) is described. No impact on the safety concerns was identified.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version number: 2.0

Approved with procedure: EMEA/H/C/004030/II/0020

Date of approval (opinion date): 09th April 2021

Qualified Person Responsible for Pharmacovigilance (QPPV) name:

[redacted]

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

[redacted]

Table of Contents

List of Tables

List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASR	Age-Standardised Rate
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
BC	Breast Cancer
BCRP	Breast Cancer Resistance Protein
BRCA	Breast Cancer Genes
C_{max}	Peak Plasma Concentration
CNS	Central Nervous System
CrCl	Creatinine Clearance
CYP	Cytochrome P450
DILI	Drug-Induced Liver Injury
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Estrogen-Responsive
ERBB	pan-erythroblastic leukaemia viral oncogene homolog
EU	European Union
FDA	US Food and Drug Administration
GD	Gestation Day
GI	Gastrointestinal
GLP	Good Laboratory Practice
HCP	Healthcare Professional
HER2	Human Epidermal growth factor Receptor 2
hERG	human Ether-à-go-go Related Gene
HRc	Hormone Receptor
IC_{50}	Concentration at which there is 50% inhibition
ILD	Interstitial Lung Disease
IP	Investigational Product
IV	Intravenous
LFT	Liver Function Test
LVEF	Left ventricular ejection fraction
MAH	Marketing authorisation holder
MDRD	Modification of diet in renal disease
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Multidrug Resistance Protein
MUGA	Multigated acquisition scan
N+C	Neratinib plus capecitabine
NOAEL	No-Observed Adverse Effect Level

NYHA	New York Heart Association
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PL	Package Leaflet
PPI	Proton-pump inhibitors
PSUR	Periodic Safety Update Report
PT	Preferred Term
QoL	Quality of Life
QPPV	Qualified Person Responsible for Pharmacovigilance
QTc	QT corrected
RMM	Risk management measures
RMP	Risk management plan
SAE	Serious adverse event
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardised meddra query
SNP	Single nucleotide polymorphism
SOC	System organ class
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
UK	United kingdom
ULN	Upper limit of normal
US(A)	United States (of America)

Part I: Product(s) Overview

Table I.1: Product Overview

Active substance **(INN or common name)**	Neratinib
Pharmacotherapeutic group (ATC Code)	Tyrosine kinase inhibitor (L01XE45)
Marketing Authorisation Holder	Pierre Fabre Médicament
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Nerlynx®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Nerlynx (neratinib) has the chemical name (E)-N-{4-[3-chloro-4-(pyrid in-2-yl methoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl}-4-(dimethylamino)but-2-enamide maleate.
	Summary of mode of action: Neratinib is a potent irreversible pan-erythroblastic leukaemia viral oncogene homolog (ERBB) tyrosine kinase inhibitor (TKI). It blocks mitogenic growth factor signal transduction through covalent, high affinity binding to adenosine triphosphate (ATP) binding site of 3 epidermal growth factor receptors (EGFRs): EGFR (encoded by ERBB1), human EGFR (HER)2 (encoded by ERBB2), and HER4 (encoded by ERBB4) or their active heterodimers with HER3 (encoded by ERBB3). This results in sustained inhibition of these growth-promoting pathways. Neratinib inhibits kinase activity through intracellular irreversible binding to a cysteine residue in the ATP binding pocket of the receptor. Neratinib binds the human epidermal growth factor receptor 2 (HER2) receptor, reduces EGFR and HER2 autophosphorylation, downstream mitogen-activated protein kinase, and autologous tumour killing signalling pathways, and potently inhibits tumour cell proliferation *in vitro*. Neratinib has antitumor activity in EGFR- and/or HER2-expressing carcinoma cell lines with a cellular concentration at which there is 50% inhibition (IC_{50}) <100 nM. In vivo, neratinib potently inhibits the growth of high or moderately HER2- and EGFR-dependent tumour xenograft models, when administered orally on a once-daily schedule.
	Important information about its composition: Not applicable.
Hyperlink to the product information	Product Information (dated 15th October 2020)

Indication(s) in the EEA	Current: Nerlynx as a single agent is indicated for the extended adjuvant treatment of adult patients with early-stage hormone-receptor-positive HER2-overexpressed/ amplified breast cancer (BC) who completed adjuvant trastuzumab-based therapy less than one year ago.
	Proposed: Not applicable.
Dosage in the EEA	Current (if applicable): The recommended dose is 240 mg (six 40 mg tablets) taken orally once daily, continuously for one year. Nerlynx should be taken with food, preferably in the morning. Patients should initiate treatment within 1 year after completion of trastuzumab therapy.
	Proposed (if applicable): Not applicable.
Pharmaceutical form and strengths	Current (if applicable): Film-coated tablet, 40 mg
	Proposed (if applicable): Not applicable
Is/will the product be patient to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Nerlynx (neratinib), as a single agent, is indicated for the extended adjuvant treatment of adult patients with early-stage hormone-receptor-positive HER2-overexpressed/amplified BC who completed adjuvant trastuzumab-based therapy less than one year ago.

HER2+ Breast Cancer

Breast cancer is the second most common cancer in the world, the most common among women, and one of the most important causes of death among them. An estimated 2.1 million BC cases were diagnosed worldwide in 2018 (World Health Organization, n.d.). It occurs all over the world; its incidence, mortality, and survival rates vary among different parts of the world. (Momenimovahed and Salehiniya, 2019) It represents 13% of all cancer cases in females in Europe (American Cancer Society, 2020b). In the United States in 2017, approximately 252,710 new cases of invasive BC and 6,341 cases of BC in situ were diagnosed (Momenimovahed and Salehiniya, 2019).

Breast cancer ranks as the second most common cause of cancer-related deaths worldwide (it is the most common for women) and accounted for 627,000 deaths in 2018 (~15% of all cancer deaths among women). While BC rates are higher among women in more developed regions, rates are increasing in nearly every region globally. (Bray et al, 2018; World Health Organization, no date)

Breast cancer is a heterogeneous disease, which can be divided into several subtypes with diverse clinical characteristics, respective sensitivity to therapy, and different prognosis. HER2 is normally overexpressed in 20% to 25% of BCs worldwide. HER2+ BC can be treated with precision cancer medicines that target the HER2 receptor. (Arteaga et al, 2011)

According to Proceedings of the National Academy of Sciences of the United States of America (Sørlie et al, 2001), the major tumour groups have been categorised as:

- **Luminal A** (estrogen-responsive [ER]-positive and/or PR-positive and HER2-negative, histological grade 1 or 2),
- **Luminal B** (ER-positive and/or PR-positive and HER2+, or ER-positive and/or PR-positive, HER2-negative, histological grade 3),
- **HER2** (ER-negative and PR-negative, and HER2+),
- **Triple-negative** (ER-negative, PR-negative, and HER2-negative), and
- **Normal-like** (varied gene expression profile).

HER2+ BC has been shown to exhibit significantly poorer outcomes than the luminal and normal-like groups. HER2+ BC has been shown to exhibit significantly poorer outcomes than the luminal and normal-like groups, although it is unclear yet why this tumour subtype exhibits more aggressive behaviour (Assi et al, 2013; Verma et al, 2012; Collins et al, 2012).

Incidence:

In 2018, more than two million cases of BC were diagnosed worldwide with an age-standardised rate (ASR) of 46.3 per 100,000 women. Breast cancer is the most common cancer for women, with more than two million new cases diagnosed (Bray et al, 2018).

Early onset BC incidence rates vary among populations and regions of the world, with an ASR for women below the age of 40 slightly higher in developed countries (8.8 per 100,000 per year) than in developing countries (5.4 per 100,000 per year) (Assi et al, 2013).

Incidence rates vary greatly worldwide from 25.9 per 100,000 women in South Central Asia to 94.2 per 100,000 women in Australia/New Zealand. The incidence rate per 100,000 women is 92.6 for Western Europe and 90.1 for Northern Europe (Bray et al, 2018).

Prevalence:

Breast cancer survival rates vary greatly worldwide, ranging from 80% or over in North America, Sweden, and Japan to around 60% in middle-income countries, and below 40% in low-income countries. (World Health Organization, n.d.)

Overexpression of human EGFR 2 (HER2), or amplification of the HER2 gene, is seen in approximately 15% to 25% of BC patients.

In a study assessing BC subtypes in women diagnosed with invasive BC in 2010 using data from 17 population-based cancer registries that participate in the Surveillance, Epidemiology, and End Results (SEER) programme, together comprising approximately 28% of the total population of the US covered by the SEER registry, 10.3% of BC cases were hormone receptor (HRc)+/HER2+ and 4.6% were HRc-negative and HER2+ (Howlader et al, 2014).

Demographics of the population in the authorised indication and risk factors for the disease:

Race/ethnicity:

In the USA between 2012 and 2016, the rate of BC was 13% in Hispanic women, 13% in Asian/Pacific Islander, 23% in non-Hispanic Black, 12% in American Indian/Alaska Native, and 10% in non-Hispanic White women (American Cancer Society, 2020a). White women are more likely to be diagnosed with BC, but Black women are more likely to die from the disease. (Yedjou et al, 2019).

In a review of the SEER Explorer database (2004-2011) of 373,563 women with invasive BC, 268,675 (71.9%) were non-Hispanic White; 34,928 (9.4%), Hispanic White; 38,751 (10.4%), Black; 25,211 (6.7%), Asian; and 5,998 (1.6%), other ethnicities. (Iqbal et al, 2015)

Risk Factors:

Breast cancer is a highly heterogeneous disease with some cases being associated with slow growth and excellent prognosis while other tumours exhibit a highly aggressive clinical course. Risk factors identified for BCs include:

- Personal and family history of BC: Presence of BC susceptibility genes (BC genes [BRCA] 1/2 and germline TP53 mutations), which are present at a higher proportion in young BC patients (Assi et al, 2013). The risk of developing BC increases for women with at least one first-degree relative diagnosed with BC (American Cancer Society, 2020a). A familial history of BC increases the risk by a factor of two or three (World Health Organization, n.d.).
- Young age at diagnosis: Younger patients present with more advanced-stage disease, have larger tumours than older women, more frequently present as lymph node positive, and have poorer survival (Assi et al, 2013; Verma et al, 2012). Basal-like carcinomas are overrepresented among younger women, and tumours in young women are more likely to be HER2+ and to overexpress EGFR (Collins et al, 2012; Verma et al, 2012). Women diagnosed with HER2+ BC tended to be younger, were less likely to drink alcohol and less likely to use hormone replacement therapy than women diagnosed with other types of BC (Kwan et al, 2009). Both tumour subgroups are generally associated with aggressive disease course.

- Aggressive tumour subtypes: HER2 and basal-like subtypes have been shown to exhibit significantly poorer outcome than the luminal and normal-like groups, with a higher growth rate and more aggressive clinical behaviour, and in a stage-independent manner, although both are associated with more advanced stage at presentation (Verma et al, 2012; Wolff et al 2013).
- Reproductive factors: Every year of breastfeeding is thought to confer a protective effect against BC (American Cancer Society, 2020a). There is a transient increase in the risk of BC in the years immediately following childbirth, likely related to exposure to endogenous steroid hormones, which may promote tumour growth and have been implicated in tumour initiation (Verma et al, 2012). Similarly, the risk of BC is slightly increased in current users of oral contraceptives as well as women within 10 years of oral contraceptive stoppage (Assi et al, 2013).
- Obesity: In postmenopausal women, obesity increases the risk of BC (1.5 times higher in overweight women and two times higher in obese women), likely because fat tissue is the largest source of oestrogen in postmenopausal women. In contrast, obesity may protect against BC before menopause. Furthermore, regular physical activity lowered the risk of BC by 10% to 20% in postmenopausal women and by 23% in premenopausal women (Assi et al, 2013; American Cancer Society, 2020a).

Natural history of the indicated condition in the population, including mortality and morbidity:

In 2018, the worldwide age-standardised mortality rate for women with BC (all types) was 13.0 per 100,000. (Bray et al, 2018).

Breast cancers associated with HER2 amplification showed a strong and statistically significant correlation between the degree of gene amplification and both time to disease relapse and survival, compared with breast tumours that do not overexpress HER2 (Slamon et al, 1987; Slamon et al, 1989).

Important comorbidities in the target population:

Important comorbidities for BC include previous cancer, diabetes, high blood pressure, myocardial infarction or heart attack, and obesity.

No specific information on comorbidities in patients with early-stage HER2-overexpressed/amplified BC was identified but is not expected to be different based on the HER2 status.

Part II: Module SII - Non-clinical part of the safety specification

A summary of key safety findings from non-clinical studies with implications for the risk profile of Nerlynx is presented below.

Table SII.2: Summary of key safety findings from non-clinical studies

Key safety findings (from non-clinical studies)	Relevance to human usage
Toxicity including: *Single-dose toxicity* The highest non-lethal dose was 2000 mg/kg in mice and 700 mg/kg in rats for oral administration. *Repeat-dose toxicity* Repeat-dose toxicity of neratinib was evaluated in dose range-finding and pivotal studies conducted in mice, rats, and dogs, by the oral route, for up to 9 months. The primary toxicities observed in the	In general, the toxicity of neratinib was similar across species. Target organ toxicity in animals has been predictive of human toxicity. Diarrhoea is an Important Identified Risk (see Part II, Module SVII.3.1.1); also refer to SmPC Sections 4.4, 4.8, and 4.9.

Table SII.2: Summary of key safety findings from non-clinical studies

Key safety findings (from non-clinical studies)	Relevance to human usage
oral toxicity studies were gastrointestinal (GI) and dermatological and were likely related to pharmacological inhibition of EGFR and ERBB2. Faecal alterations, often with histological correlate (including mixed cell inflammation, erosion, ulceration, luminal dilatation, villous atrophy, crypt abscesses) have been identified in mouse, rat, and dog repeat-dose toxicity studies. In the Good laboratory Practice (GLP) oral repeat-dose 26-week rat and 39-week dog toxicity studies there was neratinib-related mortality in rats at the dose of 30 mg/kg/day, and no neratinib-related mortality observed in dogs at doses up to 6 mg/kg/day. The no-observed adverse effect level (NOAEL) was 10 mg/kg/day in rats and 6 mg/kg/day in dogs. Effects on body weights and food consumption were present at higher dose levels. The principal target organ toxicities were observed in the GI tract (faecal alterations and mucosal/villous atrophy, inflammation, and/or erosions/ulcers in the intestines and stomach) and skin (focal abrasions associated with inflammation, necrosis, and/or serocellular crusts). Changes in haematology and clinical chemistry parameters (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] elevations) consistent with inflammation, GI mucosal atrophy, and/or decreased food consumption were also apparent. Additional pharmacological effects that were considered neratinib-related but not toxicologically significant were noted in reproductive organs (atrophy of the prostate, uterus, and male mammary gland), bone (physeal thickening), and liver (biliary epithelial cell vacuolation). Complete or partial reversibility of neratinib-related changes was observed at the end of the 28-day recovery periods in the 26-week rat study and in the 28-day dog study. No nephrotoxicity was observed in these studies.	The clinical implications of any secondary pharmacology suggested by these interactions is difficult to determine because the *in vitro* assays are simple displacement (ligand binding) assays, and do not identify whether neratinib would be an agonist or antagonist in vivo at the projected concentrations. The clinical consequences of these interactions, especially with the tachykinin receptors, is difficult to project based on extrapolating the pharmacology of these receptors and their subtypes because the role of tachykinins in controlling GI motility and secretion is not well-defined outside of the pathophysiology of diseases such as irritable bowel syndrome, which is a poorly defined, polymorphic clinical picture. While GI side effects, especially diarrhoea, are the dose-limiting clinical toxicity for neratinib, predicting the actual intralumenal concentrations of neratinib available to receptors after oral doses and the contribution of activation or inhibition of GI receptors to clinically relevant GI effects is speculative. However, as a means to help control the GI effects (namely, diarrhoea), the risk and management of diarrhoea in patients are described in the product labelling. Neratinib has the potential to affect liver function. Hepatotoxicity is an Important Identified Risk (see Part II, Module SVII.3.1.1.3); also refer to SmPC Sections 4.2, 4.4, 4.8, and 5.2.
Reproductive and developmental toxicity *Definitive GLP-fertility and embryonal development study in pregnant rats (before cohabitation through*	

Table SII.2: Summary of key safety findings from non-clinical studies

Key safety findings (from non-clinical studies)	Relevance to human usage
mating and implantation at 0, 3, 6, and 12 mg/kg/day) During and after cohabitation through Week 7 for males and through gestation day (GD) 7 for females, there were no neratinib-related clinical signs in treated males or treated females following once-daily oral gavage at 3, 6, or 12 mg/kg/day. In the treated males, there were no neratinib-related alterations in sperm parameters (motility, density, or morphology) or macroscopic changes observed in male reproductive organs. In addition, neratinib did not result in any effects on oestrous cycling in the treated females or on mating, fertility, or early embryonic survival in either sex. *Definitive GLP-embryofoetal development study in pregnant rats (GD 7 through GD 17 at 0, 5, 10, and 15 mg/kg/day)* All doses of neratinib transiently reduced mean maternal body weight gain, but only the 15 mg/kg/day dose reduced the overall mean maternal body weight gain for the dose period. Therefore, the maternal NOAEL for neratinib was 10 mg/kg/day. There were no effects on embryofoetal survival or foetal body weights, and neratinib did not produce any foetal external, visceral, or skeletal malformations or variations. Ossification site averages were comparable among the four dose groups. Therefore, the developmental NOAEL for neratinib was 15 mg/kg/day, the highest dose level tested. *GLP-pre- and postnatal development study in pregnant rats (GD 7 through Day 20 of lactation [DL20] at 5, 10, and 15 mg/kg/day)* Neratinib at doses of 10 and 15 mg/kg/day reduced overall mean maternal body weight gain and a decrease in maternal body weight was observed during the lactation period at 15 mg/kg/day. There were no effects on delivery parameters. In the F1 generation there were no clinical observations, changes in body weight, or food consumption. There was no impact on postweaning development, behavioural, or reproductive observations. There were no necropsy findings	There is no experience with Nerlynx in pregnant women. Refer to SmPC Sections 4.4 for information on administering Nerlynx to pregnant women and 4.6 for information on women of childbearing potential as well as contraception use in women and men.

Table SII.2: Summary of key safety findings from non-clinical studies

Key safety findings (from non-clinical studies)	Relevance to human usage
including male or female reproductive organs. The NOAEL was 5 mg/kg/day for maternal toxicity and in the F1 generation the NOAEL was 15 mg/kg/day.	
Definitive GLP-embryofoetal development study in pregnant New Zealand White (Crl:KBL[NZW]) rabbits (GD 7 through GD 19 at 0, 3, 6, and 9 mg/kg/day) At doses ≥6 mg/kg/day, neratinib resulted in abortions and maternal toxicity, including effects on maternal body weight gain, maternal food consumption, and clinical signs. Neratinib-related increases in embryofoetal death were observed at doses ≥6 mg/kg/day. Neratinib produced a low incidence of foetal gross external (domed head), soft tissue (dilation of the brain ventricles and a ventricular septal defect), and skeletal (misshapen anterior fontanelles and enlarged anterior and/or posterior fontanelles) abnormalities at 9 mg/kg/day. There is no identified NOAEL for development.	
Genotoxicity Neratinib was not genotoxic in the bacterial reverse mutation assays, the *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, or the in vivo mouse bone marrow micronucleus assay, in which neratinib was administered at doses of 500, 1000, or 2000 mg/kg. The standard battery of genotoxicity studies was conducted for neratinib metabolites M3, M6, M7, and M11, and was found to be negative. An evaluation of the potential genotoxicity of the neratinib metabolites M3, M6, M7, M10, and M11 was conducted via a review of the available databases and literature and through a computational toxicology assessment. The results showed no relevant structural alerts indicating mutagenic or carcinogenic potential of the neratinib metabolites.	Non-clinical data indicate that neratinib and its metabolites are not genotoxic.

Table SII.2: Summary of key safety findings from non-clinical studies

Key safety findings (from non-clinical studies)	Relevance to human usage
Carcinogenicity Carcinogenicity evaluations consist of a 26-week study in TgRasH2 transgenic mice and a 2-year oral carcinogenicity study in rats. In the TgRasH2 transgenic mice study, once-daily oral administration of neratinib was generally well tolerated with non-adverse, dose related reductions in mean body weight/mean body weight gain at 20 and 50 mg/kg/day in males and at 125 mg/kg/day in females as compared with controls. There was no neratinib-related mortality or neoplastic or non-neoplastic findings at any dose for males or females. There was a marginally higher incidence (not statistically significant) of hemangiosarcoma in the spleen in male mice dosed with neratinib 50 mg/kg/day compared with the control group but this was not considered related to neratinib. Therefore, neratinib was not considered carcinogenic in TgRasH2 transgenic mice at ≤50 mg/kg/day in males and ≤125 mg/kg/day in females. The objective of the rat carcinogenicity study was to determine the potential oncogenicity of neratinib when given orally for a minimum of 104 weeks to Sprague-Dawley rats. An interim 1-year phase was performed with toxicokinetic evaluation. The results demonstrated that once-daily oral administration of neratinib was generally well tolerated in male and female rats at levels of 1, 3, and 10 mg/kg/day for 52 weeks. There was no neratinib-related mortality or neoplastic or non-neoplastic findings at any dose for males or females. For the main phase, all surviving animals were submitted for necropsy on Week 92 to 101. The total number of early deaths (≤Week 101) in each group was similar and none of the early deaths were considered to be neratinib-related. There were no neratinib-related gross findings and no non-neoplastic or neoplastic microscopic findings. Therefore, based on these findings, neratinib was not considered carcinogenic in Sprague-Dawley rats. The final report of the rat carcinogenicity study is included in the submission.	Non-clinical data indicate that neratinib is not carcinogenic.

Table SII.2: Summary of key safety findings from non-clinical studies

Key safety findings (from non-clinical studies)	Relevance to human usage
General safety pharmacology: *Cardiovascular safety pharmacology* In an *in vitro* human ether-à-go-go (hERG) related gene assay, the IC_{50} of the rapidly-activating, delayed-rectifier cardiac potassium channel current was 1.9 µM (1,058 ng/mL). Neratinib is not likely to prolong the QT corrected (QTc) interval at the maximal clinical dose of 240 mg. The *in vitro* studies to evaluate the effects of M3, M6, and M7 on cloned hERG potassium channels expressed in human embryonic kidney cells have been completed. The results from these *in vitro* studies indicated that the IC_{50} for M3, M6 and M7 are >3µM, >3µM, and 2.2 µM respectively. These IC_{50} values are similar to the 1.9 µM for neratinib (Report 59094). Based on the human peak plasma concentration (C_{max}) and not adjusted for protein binding, the exposure ratio of the hERG assay IC_{50} to the human C_{max} is approximately 50 to 100. These ratios are within the generally accepted exposure ratio of 30 to 100, indicating that the metabolites are not likely to prolong the QTc interval at this exposure. Repeat-dose toxicity studies in mice, rats and dogs showed no changes in heart weight, and no macroscopic or microscopic findings in the heart with neratinib. Furthermore, in the 1-month and 9-month repeat-dose toxicity studies in dogs, no changes were seen in the electrocardiograms. The safety pharmacology study to evaluate effects on the cardiovascular system of M3 in dogs was completed. Based on the results of this single-dose study, NOAEL for M3 was considered to be 2 mg/kg.	Non-clinical data indicate that neratinib is not cardiotoxic.
Central nervous system pharmacology A single oral (gavage) dose of 0, 5, 25, or 100 mg/kg in male rats showed no effects on central nervous system (CNS) function. Administration of the M3 metabolite by a single intravenous (IV) bolus injection was well tolerated in rats at levels of 0, 0.3, 1, and 2 mg/kg. There were no M3-related changes in functional observational battery or in motor activity as compared with the controls. Therefore, based on these results, there were no apparent CNS effects	No effects of human CNS function are expected.

Table SII.2: Summary of key safety findings from non-clinical studies

Key safety findings (from non-clinical studies)	Relevance to human usage
of M3 when administered IV up to 2 mg/kg during this pharmacological CNS safety assessment (Report 20130868).	
Respiratory safety pharmacology A single oral (gavage) dose of 0, 5, 25, or 100 mg/kg in male rats showed no effects on respiratory function. A single IV bolus injection of M3 at doses of 0.3, 1, and 2 mg/kg had no effect on the respiratory system of the male Sprague-Dawley rat up to 24 hours post-dose (Report 6901562).	No effects on human respiratory function are expected.
Phototoxicity Repeat-dose toxicity studies in non-pigmented rats and pigmented dogs and the phototoxicity study in pigmented rats showed that neratinib is not phototoxic and does not cause any direct ocular or dermal toxicity.	Neratinib is not likely to be phototoxic.
Local tolerance Under the conditions of the test, neratinib is considered to be non-irritant to the skin of the rabbit. According to the Kay and Calandra Evaluation criteria, neratinib is considered to be a mild irritant to the ocular tissue of the rabbit and designated as Class 4. According to the US Food and Drug Administration (FDA) evaluation criteria, the test results were considered equivocal.	Neratinib does not cause any direct ocular or dermal toxicity in humans.
Mechanisms for drug interactions	
Neratinib is a cytochrome P450 (CYP)3A4/P-glycoprotein (P-gp) substrate. Experiments with HLM or human hepatocytes and CYP-selective inhibitors (ketoconazole or troleandomycin), as well as cDNA-expressed CYP isozymes, demonstrated that CYP3A4/5 was primarily responsible for production of M3 and M6 while M7 was formed primarily by FMO oxidation with some contribution from CYP3A4/5.	Ketoconazole, a strong CYP3A4/P-gp inhibitor, markedly increases the systemic concentration of neratinib in healthy patients (by 3.2- and 4.8-fold for C_{max} and area under the curve [AUC], respectively). Model-based predictions suggested that a moderate CYP3A4/strong P-gp inhibitor would markedly increase neratinib exposure (by 3.0- and 4.0-fold for C_{max} and AUC, respectively), while a moderate CYP3A4 inhibitor would moderately increase neratinib exposure (by 1.3- and 1.7-fold for C_{max} and AUC). Rifampicin, a strong CYP3A4/P-gp inducer, decreased the systemic concentration of

Table SII.2: Summary of key safety findings from non-clinical studies

Key safety findings (from non-clinical studies)	Relevance to human usage
The apparent permeability (Papp) of neratinib across Caco-2 cell cultures, determined in the presence and absence of prototypical inhibitors of P-gp (MDR1), Breast Cancer Resistance Protein (BCRP), and multidrug resistance protein (MRP) transporters demonstrated that neratinib was a substrate for P-gp and to a lesser extent, BCRP-mediated efflux.	neratinib in healthy patients (by 76% and 87% for Cmax and AUC, respectively). Sections 4.2, 4.3, 4.4 of the SmPC provide information on the effects of CYP3A4/P-gp inhibitors and inducers to the risk of neratinib pharmacokinetics (PK). Sections 4.5 and 5.2 of the SmPC provide further details.
The *in vitro* solubility of neratinib is pH dependent.	Neratinib exposures in fed patients given a single 240 mg oral dose were decreased by around 70% when given concomitantly with a proton-pump inhibitor (PPI) (lansoprazole), and around 50% when given a histamine H_2 Receptor Antagonists (ranitidine). Staggering the dose of ranitidine 2 hours after the dose of neratinib reduces the magnitude of the interaction by around 25%. Sections 4.2 and 4.4 of the SmPC provide information on the effects of substances that increase gastric pH to the risk of neratinib PK. Sections 4.5 and 5.2 of the SmPC provide further details.
Using hepatocytes or transfected cells with OATP1B1 or 1B3 demonstrated that neratinib and M6 do not appear to be substrates of uptake hepatic transporters.	The likelihood of any drug-drug interactions involving inhibitors of hepatic uptake transporters is low (Section 5.2 of the SmPC). The likelihood of any drug-drug interactions involving CYP450 isoenzymes at prescribed dosages is low (Section 5.2 of the SmPC). Clinical studies have demonstrated that there were no clinically significant differences in the exposure of patients to neratinib with or without concurrent dosing with loperamide. Sections 4.5 and 5.2 of the SmPC provide information on the effects of loperamide on neratinib PK.

Table SII.2: Summary of key safety findings from non-clinical studies

Key safety findings (from non-clinical studies)	Relevance to human usage
In human liver microsomes, neratinib did not potently inhibit the catalytic activities of CYP isozyme CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, or 3A4. Some inhibition of CYP2C19 was observed but not reproduced in the metabolism-dependent inhibition studies. Neratinib was not a metabolism-dependent inhibitor of CYP2B6, 2C9, 2C19, 2D6, or 3A4 activity in human liver microsomes but using hepatocytes, CYP3A4 metabolism-dependent inhibition, and time-dependent inhibition of CYP2B6 by neratinib could not be excluded. There was no clinically relevant direct CYP inhibition by the major metabolite M6, but metabolism-dependent inhibition of CYP3A4 and potentially CYP2C8 and CYP2C9 cannot be excluded, as well as time-dependent inhibition of CYP2B6 and CYP3A4 (only when using midazolam as substrate). At concentrations of 1.0 µM in human hepatocytes neratinib did not induce CYP1A2, 2B6, 2C9, or 3A4. The lack of induction of CYP3A4 was confirmed with a luciferase reporter gene assay.	
Neratinib inhibited P-gp-mediated efflux of digoxin. At the clinical dose of 240 mg, both systemic and luminal drug interactions between neratinib and P-gp substrates may occur.	Systemic exposure to digoxin increased by 54% for peak plasma concentration (C_{max}) and 32% for AUC in healthy patients when a single oral dose of digoxin 0.5 mg was coadministered with multiple oral doses of neratinib 240 mg compared with systemic exposure when digoxin was administered alone. Mean renal clearance of digoxin was not impacted. These data suggest that neratinib inhibits intestinal but not renal P-gp, consistent with the high intraluminal concentrations produced by multiple 240 mg oral doses of neratinib. Section 4.4 of the SmPC provides information on the effects of neratinib to the risk of P-gp substrate. Sections 4.5 and 5.2 of the SmPC provide further details.
Neratinib produced no clinically relevant *in vitro* inhibitory activity toward the uptake and efflux transporters, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and BSEP. Based on *in vitro* data, it is unlikely that, at clinical concentrations, neratinib would inhibit systemic BCRP but intestinal interaction with BCRP substrates cannot be	Sections 4.5 and 5.2 of the SmPC provide information on the effects of transporter inhibition by neratinib.

Table SII.2: Summary of key safety findings from non-clinical studies

Key safety findings (from non-clinical studies)	Relevance to human usage
excluded. The potential inhibition of transporters by the major metabolite was not studied.	
Other toxicity-related information or data	
Metabolite toxicity Neratinib pyridine N-oxide (M3) is a human neratinib metabolite that was not observed at appreciable levels in rats or dogs when given orally. Toxicity assessed in rats showed no M3-related effects on clinical signs, body weight, food consumption, ophthalmoscopy, clinical pathology, organ weights, or macroscopic or microscopic observations.	There was no M3-related toxicity. M3 and M7 were not genotoxic in an *in vitro* chromosome aberration and *in vitro* bacterial reverse mutation assay.
Non-clinical pharmacology Neratinib is a highly selective irreversible inhibitor of the ERBB kinases. Neratinib blocks the function of the EGFR receptor through decreased ligand-independent ERBB2 phosphorylation, thus affecting downstream signal transduction by ERBB2 and EGFR and blocking cell cycle progression. Neratinib preferentially inhibits proliferation in cell lines overexpressing ERBB2 and EGFR.	Neratinib has no effect on the growth of human breast carcinoma lines that express low levels of both ERBB2 and EGFR. Neratinib is considered to be specific for ERBB2 overexpressing tumours.
Circulating metabolites include M3, M6, M7, and M11.In non-clinical pharmacology studies, the neratinib metabolites M3, M6, M7, and M11 were tested in cell-based assays against cells expressing ERBB1, ERBB2 and ERBB4, and shown to have similar potencies to neratinib.	Neratinib represents the most prominent component in plasma and among circulating metabolites, none is above 8% of neratinib plus metabolite total exposure after oral administration of neratinib. Based on steady-state exposures, neratinib provides the majority of pharmacological activity (73%), with 20% provided by exposure to M6, 6% provided by M3, and negligible contribution (<1%) from M7 and M11 AUC.

Conclusions on non-clinical data

Safety concerns based on non-clinical data that have been confirmed by clinical data, or have not been adequately refuted by clinical data, or which are of unknown significance are presented in Table SII.3.

Table SII.3: List of safety concerns from non-clinical data

Safety concerns
Important identified risks (confirmed by clinical data) • Gastrointestinal toxicity • Hepatotoxicity
Important potential risks (not refuted by clinical data or which are of unknown significance) • Reproductive and developmental toxicity

Part II: Module SIII - Clinical trial exposure

Clinical study exposure

The majority of patients have received Nerlynx orally 240 mg once per day. Across the development programme for Nerlynx, patients have received neratinib at doses ranging from 40 mg to 800 mg per day.

Exposure in randomised studies

The randomised blinded clinical study population only includes the pivotal study ExteNET (Extended Adjuvant Treatment with Neratinib; 3144A2-3004-WW). This study is described in Annex 2.

The trial 3144A2-3004-WW comprised the randomised clinical study population and included 2,840 patients; 1,420 patients randomised to neratinib and 1,420 patients randomised to receive placebo. A total of 24 patients (12 in each treatment arm) did not receive the investigational product (IP); 1,408 patients received neratinib and 1,408 received placebo.

- Exposure to Nerlynx: 965.71 patient-years. In this trial, 191 patients received at least 12 months of treatment (Table SIII.4 and Table SIII.5).
- 1,236 patients were 18 to 64 years of age; 147 were 65 to 74 years of age, and 25 were 75 years of age or older (Table SIII.6).
- Most patients were White (1,156 patients); 188 patients were Asian; 25 were Black or African American; and 39 were of Other ethnic/racial origin (Table SIII.7).
- Renal impairment (measured by creatinine clearance [CrCl]) at baseline: 297 patients had mild (CrCl >50 to <80 mL/min), and 17 had moderate renal impairment (estimated CrCl >30 and <50 mL/min); no patients had severe (CrCl ≤30 mL/min) renal impairment at baseline (Table SIII.8).
- Liver function abnormality at baseline: there were eight patients with ALT >2.5 and ≤5.0 times the upper limit of normal (×ULN); no patients had ALT >5.0×ULN at baseline; one patient had AST >2.5 and ≤5.0×ULN; no patients had AST >5.0×ULN. There were three patients with bilirubin levels >1.5 to ≤3.0×ULN; no patients had bilirubin levels >3.0 to ≤10×ULN. There were 27 patients with alkaline phosphatase (ALP) >2.5 to ≤5.0×ULN; no patients had ALP >5.0 to ≤20×ULN (Table SIII.8).

Table SIII.4: Patient treatment exposure by duration in randomised blinded study population (Safety Population)

Indication	<1 Month n	≥1 Month n	≥3 Months n	≥6 Months n	≥9 Months n	≥12 Months n (patient-years)	Total n (patient-years)
Monotherapy breast cancer (ExteNET study)	262	1,146	1,029	933	883	191 (194.01)	1,408 (965.71)

Safety population includes all patients who received at least one dose of neratinib.
Month is defined as exposure days/(365.25/12).
Program: Y:\stat\neratinib\meta\nda_ebc\iss\csr\program\rmp\t_ex_ptyr.sas
Output: t01-01-01-ex-ptyy-mon-db.rtf (Date Generated: 19JAN2016:16:56) Source: adsl

Table SIII.5: Duration of exposure by dose level in randomised blinded study population (Safety Population)

Dose of exposure (mg/day)	n (patient-years)
Monotherapy breast cancer (ExteNET study)	
240	1,408 (965.71)

Safety population includes all patients who received at least one dose of neratinib.
Dose level is based on initial planned dose.
Program: Y:\stat\neratinib\meta\nda_ebc\iss\csr\program\rmp\t_ex_ptyr.sas
Output: t01-02-02-ex-ptyr-doselv-db.rtf (Date Generated: 19JAN2016:16:56) Source: adsl

Table SIII.6: Exposure by age group and gender in randomised blinded study population (Safety Population)

Monotherapy breast cancer (ExteNET study)		
	Gender	
Age group	Male n (patient-years)	Female n (patient-years)
18 to 64 years	0 (0.00)	1,236 (874.28)
65 to 74 years	0 (0.00)	147 (80.03)
≥75 years	0 (0.00)	25 (11.41)
Total	0 (0.00)	1,408 (965.71)

Safety population includes all patients who received at least one dose of neratinib.
Program: Y:\stat\neratinib\meta\nda_ebc\iss\csr\program\rmp\t_ex_ptyr.sas
Output: t01-03-02-ex-ptyr-agesex-db.rtf (Date Generated: 19JAN2016:16:56) Source: adsl

Table SIII.7: Exposure by ethnic or racial origin in randomised blinded study population (Safety Population)

Ethnic/racial origin	n (patient-years)
Monotherapy breast cancer (ExteNET study)	
White	1,156 (789.34)
Black or African American	25 (12.10)
Asian	188 (135.58)
Other	39 (28.69)
Unknown	0 (0.00)

Safety population includes all patients who received at least one dose of Neratinib.
Program: Y:\stat\neratinib\meta\nda_ebc\iss\csr\program\rmp\t_ex_ptyr.sas
Output: t01-04-02-ex-ptyr-race-db.rtf (Date Generated: 19JAN2016:16:56) Source: adsl

Table SIII.8: Exposure by renal and liver function in randomised blinded study population (Safety Population)

	Exposure n (patient-years)
Renal impairment at baseline	
Normal (CrCl ≥80 mL/min)	1,047 (742.24)
Mild (CrCl >50 to <80 mL/min)	297 (183.46)
Moderate (CrCl >30 to ≤50 mL/min)	17 (8.85)
Severe (CrCl ≤30 mL/min)	0 (0.00)
Missing	47 (31.16)
Total	1,408 (965.71)

Table SIII.8: Exposure by renal and liver function in randomised blinded study population (Safety Population)

	Exposure n (patient-years)
Liver function abnormality at baseline	
ALT	
≤ULN (normal)	1,252 (865.32)
>ULN to ≤2.5xULN	144 (92.71)
>2.5 to ≤5.0xULN	8 (5.07)
>5.0 to ≤20xULN	0 (0.00)
>20xULN	0 (0.00)
Missing	4 (2.61)
Total	1,408 (965.71)
AST	
≤ULN (normal)	1,324 (906.97)
>ULN to ≤2.5xULN	77 (54.45)
>2.5 to ≤5.0xULN	1 (0.01)
>5.0 to ≤20xULN	0 (0.00)
>20xULN	0 (0.00)
Missing	6 (4.28)
Total	1,408 (965.71)
Bilirubin	
≤ULN (normal)	1,339 (912.77)
>ULN to ≤1.5xULN	61 (47.33)
>1.5 to ≤3.0xULN	3 (2.94)
>3.0 to ≤10xULN	0 (0.00)
>10 x ULN	0 (0.00)
Missing	5 (2.67)
Total	1,408 (965.71)
Alkaline phosphatase	
≤ULN (normal)	1,176 (803.29)
>ULN to ≤2.5xULN	200 (144.27)
>2.5 to ≤5.0xULN	27 (16.43)
>5.0 to ≤20xULN	0 (0.00)
>20xULN	0 (0.00)
Missing	5 (1.73)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CrCl = creatinine clearance; ULN = upper limit of normal.
Safety population includes all patients who received at least one dose of neratinib.
Randomised Blinded Study includes ExteNET Study only.
Program: Y:\stat\neratinib\meta\nda_ebc\iss\csr\program\rmp\t_ex_ptyr_renal_liver.sas
Output: t01-05-02-ex-ptyr-renal-liver-db.rtf (Date Generated: 21JAN2016:15:30) Source: adsl

Exposure in all clinical studies

The All Clinical Study Population includes patients who received at least one dose of neratinib in the following studies:

- Monotherapy BC: including non-randomised studies 3144A1-201-WW, and PUMA-NER-6201, and randomised studies 3144A2-3004-WW and 3144A2-3003-WW
- Monotherapy in solid tumours includes: Studies 3144A1-102-US, 3144A1-104-JA, 3144A1-200-WW, PUMA-NER-4201 (Neratinib Arm), PUMA-NER-5201
- Combination: Studies 3144A1-202-WW, 3144A1-203-WW, 3144A2-1115-JA, 3144A2-1118-JA, 3144A1-1122-JA, 3144A1-2204-WW, 3144A1-2205-WW, 3144A1-2206-WW, 3144A2-3005-WW, PUMA-NER-4201 (Combination Arm), 10-005; PUMA-NER-1301
- Healthy Volunteers: Studies 3144A1-105-US, 3144A1-106-US, 3144A1-107-US, 3144A1-1108-US, 3144A1-1109-US, 3144A1-1110-US, 3144A1-1111-US, 3144A1-1116-US, 3144A1-1117-US, 3144A1-1119-US, 3144A1-1127-WW, PUMA-NER-0101

These studies are described in Annex 2.

A total of 4,346 patients received neratinib. The All Clinical Studies Population includes patients who were administered doses ranging from 40 mg/day to 800 mg/day (Table S.III.9).

Exposure to neratinib in the All Clinical Study Population is summarised in the following tables for all patients by indication, duration, dose level, age group, gender, and ethnic or racial origin.

Table S.III.9: Patient treatment exposure by indication and duration in all clinical studies (Safety Population)

Indication	<1 Month n	≥1 Month n	≥3 Months n	≥6 Months n	≥9 Months n	≥12 Months n (patient-years)	Total n (patient-years)
Monotherapy breast cancer	394	1,861	1,629	1,439	1,340	356 (430.84)	2,255 (1,576.30)
Monotherapy solid tumours	112	410	207	82	49	26 (44.32)	522 (166.10)
Combination therapy	96	1,205	909	662	442	312 (718.29)	1,301 (1,105.50)
Healthy volunteers	401	38	0	0	0	0 (0.00)	439 (22.06)
Total	1,003	3,514	2,745	2,143	1,831	694 (1,193.40)	4,517 (2,869.90)

Safety population includes all patients who received at least one dose of neratinib.
Month is defined as exposure days/(365.25/12).
Monotherapy breast cancer includes studies: 3144A1-201-WW, 3144A2-3003-WW, 3144A2-3004-WW, and PUMA-NER-6201, PUMA-NER-5201 (Neratinib Arm)
Monotherapy in solid tumours includes studies: 3144A1-102-US, 3144A1-104-JA, 3144A1-200-WW, PUMA-NER-4201 (Neratinib Arm), PUMA-NER-5201 (Neratinib Arm)
Combination studies include: 3144A1-202-WW, 3144A1-203-WW, 3144A2-1115-JA, 3144A2-1118-JA, 3144A1-1122-JA, 3144A1-2204-WW, 3144A1-2205-WW, 3144A1-2206-WW, 3144A2-3005-WW, PUMA-NER-4201 (Combination arm), PUMA-NER-5201 (Combination arm), 10-005
Healthy Volunteers: 3144A1-105-US, 3144A1-106-US, 3144A1-107-US, 3144A1-1108-US, 3144A1-1109-US, 3144A1-1110-US, 3144A1-1111-EU, 3144A1-1116-US, 3144A1-1117-US, 3144A1-1119-US, 3144A1-1127-US, PUMA-NER-0101, PUMA-NER-0102, PUMA-NER-0103, PUMA-NER-0104, PUMA-NER-0105.
Program: Y:\stat\neratinib\meta\rmp2020\csr\program\tables\t-ex-ptyy-mon-all.sas
Output: t01-01-02-ex-ptyy-mon-all.rtf (Date Generated: 08JUN2020:15:09) Source: adam.adsl

Table SIII.10: Duration of exposure by dose level and indication in all clinical studies (Safety Population)

Dose of exposure (mg/day)	n (patient-years)
Monotherapy breast cancer	
240	2,255 (1,576.30)
Total	2,255 (1,576.30)
Monotherapy solid tumours	
40	3 (0.63)
80	7 (1.37)
120	4 (1.16)
160	3 (0.67)
180	6 (2.34)
240	403 (129.18)
320	90 (28.71)
400	6 (2.030)
Total	522 (166.10)
Combination therapy	
120	17 (6.43)
160	54 (19.66)
200	24 (7.13)
240	1,206 (1,072.2)
Total	1,301 (1,105.5)
Healthy volunteers	
120	33 (0.09)
200	6 (0.02)
240	370 (21.87)
400	12 (0.03)
640	12 (0.03)
800	6 (0.02)
Total	439 (22.06)

Table SIII.10: Duration of exposure by dose level and indication in all clinical studies (Safety Population)

Dose of exposure (mg/day)	n (patient-years)
Overall total	
40	3 (0.63)
80	7 (1.37)
120	54 (7.67)
160	57 (20.33)
180	6 (2.34)
200	30 (7.15)
240	4,234 (2,799.50)
320	90 (28.71)
400	18 (2.07)
640	12 (0.03)
800	6 (0.02)
Total	4,517 (2,869.90)

Safety population includes all patients who received at least one dose of neratinib.
Monotherapy breast cancer includes studies: 3144A1-201-WW, 3144A2-3003-WW, 3144A2-3004-WW, and PUMA-NER-6201, PUMA-NER-5201 (Neratinib Arm)
Monotherapy in solid tumours includes studies: 3144A1-102-US, 3144A1-104-JA, 3144A1-200-WW, PUMA-NER-4201 (Neratinib Arm), PUMA-NER-5201 (Neratinib Arm)
Combination studies include: 3144A1-202-WW, 3144A1-203-WW, 3144A2-1115-JA, 3144A2-1118-JA, 3144A1-1122-JA, 3144A1-2204-WW, 3144A1-2205-WW, 3144A1-2206-WW, 3144A2-3005-WW, PUMA-NER-4201 (Combination arm), PUMA-NER-5201 (Combination arm), 10-005
Healthy Volunteers: 3144A1-105-US, 3144A1-106-US, 3144A1-107-US, 3144A1-1108-US, 3144A1-1109-US, 3144A1-1110-US, 3144A1-1111-EU, 3144A1-1116-US, 3144A1-1117-US, 3144A1-1119-US, 3144A1-1127-US, PUMA-NER-0101, PUMA-NER-0102, PUMA-NER-0103, PUMA-NER-0104, PUMA-NER-0105.
Program: Y:\stat\neratinib\meta\rmp2020\csr\program\tables\t-ex-ptyr-doselv-all.sas
Output: t01-02-01-ex-ptyr-doselv-all.rtf (Date Generated: 08JUN2020:13:33) Source: adam.adsl

Table SIII.11: Exposure by indication, age group, and gender in all clinical studies (Safety Population)

Age group	Male n (patient-years)	Female n (patient-years)
Monotherapy breast cancer		
18 to 64 years	4 (2.00)	1,968 (1,413.9)
65 to 74 years	0 (0.00)	234 (134.01)
≥75 years	1 (1.00)	48 (25.32)
Total	5 (3.00)	2,250 (1,573.3)
Monotherapy solid tumours		
18 to 64 years	132 (43.66)	222 (71.43)
65 to 74 years	48 (13.11)	71 (22.74)
≥75 years	28 (9.63)	21 (5.52)
Total	208 (66.40)	314 (99.69)
Combination therapy		
18 to 64 years	64 (17.06)	978 (889.78)
65 to 74 years	30 (9.57)	175 (151.55)
≥75 years	6 (1.77)	48 (35.73)
Total	100 (28.40)	1,201 (1,077.1)

Table SIII.11: Exposure by indication, age group, and gender in all clinical studies (Safety Population)

Age group	Male n (patient-years)	Female n (patient-years)
Healthy volunteers		
18 to 64 years	385 (19.37)	54 (2.68)
65 to 74 years	0 (0.00)	1 (0.00)
Total	385 (19.37)	53 (2.68)
Total		
18 to 64 years	585 (82.09)	3,221 (2,377.8)
65 to 74 years	78 (22.69)	481 (308.30)
≥75 years	35 (12.40)	117 (66.57)
Total	698 (117.18)	3,819 (2,752.7)

Safety population includes all patients who received at least one dose of neratinib.
Monotherapy breast cancer includes studies: 3144A1-201-WW, 3144A2-3003-WW, 3144A2-3004-WW, and PUMA-NER-6201, PUMA-NER-5201 (Neratinib Arm)
Monotherapy in solid tumours includes studies: 3144A1-102-US, 3144A1-104-JA, 3144A1-200-WW, PUMA-NER-4201 (Neratinib Arm), PUMA-NER-5201 (Neratinib Arm)
Combination studies include: 3144A1-202-WW, 3144A1-203-WW, 3144A2-1115-JA, 3144A2-1118-JA, 3144A1-1122-JA, 3144A1-2204-WW, 3144A1-2205-WW, 3144A1-2206-WW, 3144A2-3005-WW, PUMA-NER-4201 (Combination arm), PUMA-NER-5201 (Combination arm), 10-005
Healthy Volunteers: 3144A1-105-US, 3144A1-106-US, 3144A1-107-US, 3144A1-1108-US, 3144A1-1109-US, 3144A1-1110-US, 3144A1-1111-EU, 3144A1-1116-US, 3144A1-1117-US, 3144A1-1119-US, 3144A1-1127-US, PUMA-NER-0101, PUMA-NER-0102, PUMA-NER-0103, PUMA-NER-0104, PUMA-NER-0105.
Program: Y:\stat\neratinib\meta\rmp2020\csr\program\tables\t-ex-ptyr-agesex-all.sas
Output: t01-03-01-ex-ptyr-agesex-all.rtf (Date Generated: 09JUN2020:10:31) Source: adam.adsl

Table SIII.12: Exposure by indication and ethnic or racial origin in all clinical studies (Safety Population)

Ethnic/racial origin	n (patient-years)
Monotherapy breast cancer	
White	1,775 (1,193.2)
Black or African American	69 (43.13)
Asian	290 (242.57)
American Indian or Alaska Native	2 (2.00)
Native Hawaiian or other Pacific Islander	4 (3.21)
Other	90 (66.39)
Unknown	5 (3.29)
Monotherapy solid tumours	
White	423 (129.80)
Black or African American	14 (4.02)
Asian	55 (20.09)
American Indian or Alaska Native	2 (0.32)
Other	13 (3.03)
Unknown	6 (2.17)

Table SIII.12: Exposure by indication and ethnic or racial origin in all clinical studies (Safety Population)

Ethnic/racial origin	n (patient-years)
Combination therapy	
White	763 (542.97)
Black or African American	43 (30.63)
Asian	415 (497.32)
American Indian or Alaska Native	1 (0.14)
Native Hawaiian or other Pacific Islander	1 (0.13)
Other	56 (26.64)
Unknown	5 (2.82)
Healthy Volunteers	
White	317 (15.20)
Black or African American	95 (5.29)
Asian	5 (0.18)
American Indian or Alaska Native	1 (0.04)
Other	17 (1.23)
Multiple	4 (0.12)
Overall total	
White	3,278 (1,881.2)
Black or African American	221 (83.08)
Asian	765 (760.17)
American Indian or Alaska Native	6 (2.50)
Native Hawaiian or other Pacific Islander	5 (3.34)
Other	176 (97.28)
Unknown	16 (8.29)
Multiple	4 (0.12)

Safety population includes all patients who received at least one dose of neratinib.
Monotherapy breast cancer includes studies: 3144A1-201-WW, 3144A2-3003-WW, 3144A2-3004-WW, and PUMA-NER-6201, PUMA-NER-5201 (Neratinib Arm)
Monotherapy in solid tumours includes studies: 3144A1-102-US, 3144A1-104-JA, 3144A1-200-WW, PUMA-NER-4201 (Neratinib Arm), PUMA-NER-5201 (Neratinib Arm)
Combination studies include: 3144A1-202-WW, 3144A1-203-WW, 3144A2-1115-JA, 3144A2-1118-JA, 3144A1-1122-JA, 3144A1-2204-WW, 3144A1-2205-WW, 3144A1-2206-WW, 3144A2-3005-WW, PUMA-NER-4201 (Combination arm), PUMA-NER-5201 (Combination arm), 10-005
Healthy Volunteers: 3144A1-105-US, 3144A1-106-US, 3144A1-107-US, 3144A1-1108-US, 3144A1-1109-US, 3144A1-1110-US, 3144A1-1111-EU, 3144A1-1116-US, 3144A1-1117-US, 3144A1-1119-US, 3144A1-1127-US, PUMA-NER-0101, PUMA-NER-0102, PUMA-NER-0103, PUMA-NER-0104, PUMA-NER-0105.
Program: Y:\stat\neratinib\meta\rmp2020\csr\program\tables\t-ex-ptyr-race-all.sas
Output: t01-04-01-ex-ptyr-race-all.rtf (Date Generated: 08JUN2020:13:30) Source: adam.adsl

Part II: Module SIV - Populations not studied in clinical trials

Clinical development programmes are restricted to the enrolled study population eligible under the protocol specified inclusion and exclusion criteria. The following information outlines limitations of the programme in generalising the safety observations of the Phase 2/3 studies with Nerlynx to the patients in the expected target indication.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table SIV.13: Exclusion criteria that will remain as contraindications

Criteria	Implications for target population
Hypersensitivity to the active substance or any of the excipients	In SmPC Section 4.3 provides information on Nerlynx contraindications including hypersensitivity to the active substance or to any of the excipients listed in SmPC Section 6.1.

Abbreviations: SmPC =: Summary of Product Characteristics.

Table SIV.14: Exclusion criteria that are not proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
• Pregnancy and breastfeeding	• Studies in animals have shown embryofoetal lethality and foetal morphological anomalies. • It is not known whether neratinib is excreted in human milk. A risk to the breastfed infant cannot be excluded.	• Special warnings and precautions for use are provided in the SmPC. • SmPC Section 4.4 provides information that Nerlynx may cause foetal harm. • SmPC Section 4.6 provides information regarding contraception use in women of childbearing potential and in men, and that it is not known whether Nerlynx is excreted in human milk, that a risk to the breastfed infant cannot be excluded, and that a decision must be made whether to discontinue breastfeeding or to discontinue Nerlynx, taking into account the importance of Nerlynx to the mother and the benefit of breastfeeding to the child.
• Symptomatic or unstable CNS metastases	• Patients with brain metastases are routinely excluded from clinical trials testing new anticancer agents, due to poor Eastern Cooperative Oncology Group (ECOG) status, prognosis, life expectancy, or lack of intact blood-brain barrier.	• CNS recurrence was reduced in the Nerlynx group compared with placebo, although this finding was not statistically significant.

Table SIV.14: Exclusion criteria that are not proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
• Presence of clinically significant or uncontrolled cardiac disease, including congestive heart failure (NYHA functional classification of ≥2), angina requiring treatment, myocardial infarction within the past 12 months, or any clinically significant supraventricular arrhythmia or ventricular arrhythmia requiring treatment or intervention	• A stable selected population was required for the clinical trial population at baseline to reduce any confounding factors. Patients with clinically significant heart disease were excluded.	• Compared with placebo, Nerlynx was not associated with an increase in cardiac-associated adverse reactions, grade 3 cardiac toxicities, and left ventricular ejection fraction (LVEF)decrease (see Part II: SVII.3.1.2, and information regarding LVEF in SmPC Section 4.4).
• Presence of secondary malignancy	• Patients with secondary malignancies were excluded from clinical studies to reduce confounding effects.	• In the ExteNET trial, the frequency of AEs in the System Organ Class (SOC) Neoplasms benign, malignant and unspecified (including cysts and polyps) was 2.1% for both Nerlynx- and placebo-treated patients; most of these events were related to progressive breast disease or benign neoplasms. • Compared with placebo, Nerlynx was not associated with an increase in the risk for secondary malignancy.
• Renal impairment • (Creatinine >1.5 × ULN or Calculated CrCl <50 mL/min [Cockcroft-Gault formula or Modification of Diet in Renal Disease (MDRD) formula])	• This is a typical precautionary measure applied in clinical trial patients when a drug has not been widely used in humans.	• There is no experience with Nerlynx in patients with severe renal impairment. In patients with mild or moderate renal impairment (CrCl 30 to 80 mL/min) compared with normal renal function (CrCl >80 mL/min), treatment-emergent AEs and serious TEAEs were reported at the same frequency in the Nerlynx and placebo groups. Discontinuations were higher in the mild renal impairment patients (37.0% vs 6.6%, Nerlynx vs placebo, respectively)

Table SIV.14: Exclusion criteria that are not proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
		compared with patients with normal renal function (24.5% vs 5.2%) due to diarrhoea and dehydration. • Renal impairment is unlikely to affect the PK of Nerlynx given that the percentage of neratinib excreted in the urine is less than 0.5%.
• QTc interval >450 ms for men or 470 ms for women	• Cardiac AEs have the potential for serious and irreversible morbidity and thus have a broad impact on study conduct.	• Results of a study with healthy patients to assess the effects of neratinib on cardiac conduction showed that neratinib was not associated with prolongation of the QTc interval in humans at the recommended dose of 240 mg daily. • The SmPC Section 4.4 includes recommendations to monitor patients with known cardiac risk factors.
• Significant chronic GI disorder with diarrhoea as a major symptom (e.g., Crohn's disease, ulcerative colitis, malabsorption, or grade ≥2 diarrhoea of any aetiology at baseline)	• Diarrhoea is a known adverse reaction to treatment with neratinib. A stable population was required for clinical study population at baseline to reduce confounding factors.	• Diarrhoea can be managed by prophylactic treatment with loperamide and dose modification. • The SmPC Section 4.4 describes the management of diarrhoea with recommendations for the prophylactic treatment with an antidiarrheal medicinal product during the first 1-2 months of Nerlynx treatment. Guidelines for adjusting doses of Nerlynx in the setting of diarrhoea are also provided in SmPC Section 4.2.
• Haemoglobin <8 g/dL (transfusion allowed to treat low haemoglobin); transfusion must be at least 7 days prior to start of treatment	• Non-clinical data demonstrated that neratinib caused a decrease in red cell mass parameters (red blood cell, haemoglobin, and haematocrit). A stable population was required for clinical study population at baseline to reduce confounding factors.	• Haematological toxicities were reported at a low frequency (7.1% in Nerlynx-treated patients vs 3.4% in placebo-treated patients) and were mostly mild in severity. There is no evidence that Nerlynx is associated with severe or serious haematologic toxicity.

Table SIV.14: Exclusion criteria that are not proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
• Abnormal liver test value concentrations consisting of any of the following: • Total bilirubin >1.5×ULN • AST or ALT >2.5×ULN (>5×ULN if liver metastases are present)	• A stable selected population was required for the clinical study population at baseline to reduce any confounding factors.	• Severe hepatic impairment (Child Pugh C) is contraindicated (SmPC Section 4.3). In a PK study of non-oncology patients with severe pre-existing hepatic impairment (Child Pugh C), the clearance of neratinib was decreased by 36% and exposure to neratinib increased by about 3-fold as compared with healthy patients (SmPC Sections 4.2 and 5.2). ALT increased and AST increased are expected ADRs per SmPC Section 4.8.

Abbreviations: ADR = adverse drug reaction; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; ExteNET = Extended Adjuvant Treatment of Breast Cancer with Neratinib; GI = gastrointestinal; LVEF = left ventricular ejection fraction; MDRD = modification of diet in renal disease; NYHA = New York Heart Association; QTc = QT corrected; SmPC = Summary of Product Characteristics; SOC = system organ class; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Table SIV.15: Limitations to detect adverse reactions in clinical trial development programmes

Ability to detect adverse reactions	Limitation of study programme	Discussion of implications for target population
Due to rare occurrence	Rare ADRs may not have been detected in clinical studies due to limited exposure.	Routine pharmacovigilance surveillance will be in place to detect rare ADRs.
Due to prolonged exposure longer than was studied in the clinical studies	A total of 665 patients received treatment for 12 or more months in the All Clinical Study Population.	Routine pharmacovigilance activities and signal detection will allow the identification of reactions that may not have been detected in clinical studies.
Due to cumulative effects	Duration of exposure, hence cumulative dose, was limited due to expected early progression of disease in the study population.	Limited impact. Cumulative effects in real-life use in the proposed indication are not expected to be longer than in clinical trials.
Due to long latency period	Duration of exposure was limited due to expected early progression of disease in the study population.	Limited impact.

Abbreviations: ADR = adverse drug reaction.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Children

Nerlynx is not indicated for use in the paediatric population. A product-specific class waiver on conditions pursuant to Article 12 and on review of waivers pursuant to Article 14 of Regulation (EC)1901/2006 as amended has been granted for treatment of breast cancer on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as BC is not a disease of the child, and clinical studies(s) are not feasible.

Elderly

In the ExteNET trial, the mean age of the Safety Population was 52.3 years in the Nerlynx arm, 1,236 patients were less than 65 years of age, 172 were ≥65 years of age, of whom 25 were 75 years or older.

Frequencies of AEs, SAEs, and treatment-emergent AEs (TEAEs) in patients less than 65 years of age and those aged 65 years and older are presented in Table SIV.16.

Table SIV.16: Summary of adverse reactions in the elderly population (ExteNET study)

Category		Age group	
		<65 years	≥65 years
Treatment discontinuation due to adverse reactions	Nerlynx	25.2%	44.8%
	Placebo	5.3%	6.4%
Serious adverse reactions	Nerlynx	7.0%	9.9%
	Placebo	5.7%	8.1%
Treatment-emergent adverse reactions leading to hospitalisation	Nerlynx	6.3%	8.7%
	Placebo	4.9%	8.1%

Source: Clinical Study Report Tables 158 and 159, Source 14.3.1.1.1 and 14.3.1.1.2

In the Nerlynx arm, there was a higher frequency of treatment discontinuations due to adverse reactions in patients aged 65 years and older than in patients less than 65 years old.

The serious adverse reactions most frequently reported in patients aged 65 years and older were vomiting (4 patients [2.3%]), diarrhoea (3 patients [1.7%]), dehydration (2 patients [1.2%]), and renal failure (2 patients [1.2%]).

There are no specific safety concerns for elderly patients at this time. The Applicant will continue to monitor safety in patients who are 65 years of age or older to ensure the benefit-risk balance remains positive in this group. Review of applicable safety information will be provided routinely in periodic safety update reports (PSURs).

Pregnant or breastfeeding women

Pregnancy and breastfeeding are not recommended.

There is no experience with Nerlynx in pregnant or lactating women. There were no effects on mating or the ability of animals to get pregnant, but embryofoetal lethality and foetal morphologic anomalies (e.g., domed head, dilation of brain ventricles, and misshapen anterior fontanelles and enlarged anterior and/or posterior fontanelles) were observed.

No cases of exposure to neratinib during pregnancy were reported.

Women should avoid becoming pregnant while taking Nerlynx and for up to one month after ending treatment. Women of childbearing potential must use highly effective contraceptive measures during treatment and for one month after the end of therapy; women using systemically acting hormonal contraceptives should add a barrier method.

It is not known whether neratinib is excreted in human milk. A risk to newborns/infants cannot be excluded. No cases of exposure to neratinib during lactation were reported.

Patients with hepatic impairment

Exposure in patients and patients according to hepatic impairment is discussed in Part II, Module SIII.

In Trial 3144A1-1111-EU/B1891009, the PK profile and safety and tolerability of neratinib were assessed in non-cancer patients with various levels of chronic hepatic impairment (Child-Pugh classes A, B, and C, 6 patients in each group) and matched healthy adults (9 patients). Treatment-emergent adverse events were reported in 7 (25.9%) patients: 2 (33.3%) in the Child-Pugh B group, 3 (50.0%) in the Child-Pugh C group, and 2 (33.3%) in matched healthy patients. The most commonly reported TEAEs were diarrhoea and haematuria, each reported by two patients (33.3%) in the Child-Pugh C group. All TEAEs reported in this study were of mild intensity. There were no reports of serious adverse events (SAEs), adverse events (AEs) leading to withdrawal, or deaths.

The PK profile was assessed after a single 120 mg dose of neratinib up to 72 hours after administration. Results from this study showed C_{max} and AUC in the Child-Pugh A and Child-Pugh B patients not to be different from the concentration in healthy adults. In the Child-Pugh C patients, C_{max} was approximately 2.73-fold and AUC was approximately 2.81-fold that in healthy patients. The oral clearance of neratinib decreased by about 36% in the Child-Pugh C patients as compared with healthy patients. The elimination half-life of neratinib in the Child-Pugh C patients increased 3-fold as compared with the healthy patients.

Patients with renal impairment

Exposure in patients and patients with renal impairment is discussed in Part II, Module SIII.

There is no experience with Nerlynx in patients with severe renal impairment. However, renal impairment is unlikely to affect the PK of Nerlynx given that the percentage of neratinib excreted in the urine is less than 0.5%.

In the ExteNET trial, patients with mild or moderate renal impairment (CrCl 30-80 mL/min) compared with normal renal function (CrCl >80 mL/min) TEAEs and serious TEAEs were reported at the same frequency. Discontinuations were higher in the mild renal impairment patients (37.0% vs 6.6%) or moderate renal impairment (41.2% vs 5.6%) compared with patients with normal renal function (24.5% vs 5.2%, neratinib vs placebo, respectively) due to diarrhoea and dehydration.

Patients with other relevant comorbidity

Cardiovascular disease

Patients with clinically significant or uncontrolled cardiac disease, including congestive heart failure (New York Heart Association [NYHA] functional classification of ≥2), angina requiring treatment myocardial infarction within the past 12 months, or any clinically significant supraventricular arrhythmia or ventricular arrhythmia requiring treatment or intervention were excluded from clinical studies.

Results from non-clinical and clinical studies did not indicate that there was a risk of cardiotoxicity. However, there is no experience with Nerlynx in patients with significant or uncontrolled cardiac disease.

Subpopulation carrying known and relevant polymorphism

Genome-wide association studies were published in the 2000s that investigated the presence of ERBB2 single nucleotide polymorphism (SNP) and any association to increased risk of BC. These

studies were performed in different ethnic populations (90 Korean women, 4,449 British women, and 1,950 Han Chinese women) and with different methodologies and did not identify any SNPs with significant association with BC (Han et al, 2005; Benusiglio et al, 2005; Benusiglio et al, 2006; Breyer et al, 2009). The study by Breyer et al (2009) identified a tandem repeat variant in the ERBB2 promoter that was thought to increase protein expression rather than gain or switch function of the ERBB2 protein. No further large-scale population studies investigating germline ERBB2 variants and risk of BC have been reported. However, given the negative results from these previous studies, the possibility of identifying a pathogenic germline variant with a relevant population frequency is unlikely.

Subpopulation with different hormonal receptor status

Nerlynx, as a single agent, is indicated for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified BC who have received prior adjuvant trastuzumab-based therapy. HER2+ BC tumours may or may not express oestrogen receptors and/or progesterone receptors.

As Nerlynx is a highly selective inhibitor of the ERBB kinases, the hormonal receptor status of the tumour is unlikely to affect the safety profile of Nerlynx.

Patients of different racial and/or ethnic origin

Exposure in patients according to racial and/or ethnic origin is discussed in Part II: Module SIII. Most of the patients in the clinical trial population were White.

Table SIV.17: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	There is no experience with Nerlynx in pregnant or lactating women. There were no effects on mating or the ability of animals to get pregnant, but embryofoetal lethality and foetal morphologic anomalies (e.g., domed head, dilation of brain ventricles, and misshapen anterior fontanelles and enlarged anterior and/or posterior fontanelles) were observed. No cases of exposure to neratinib during pregnancy were reported.
Children	Paediatric studies are not included in the clinical development program. Nerlynx is not indicated for use in the paediatric population.
Elderly	In the ExteNET trial, the mean age of the Safety Population was 52.3 years in the Nerlynx arm, 1,236 patients were less than 65 years of age, 172 were ≥65 years of age, of whom 25 were 75 years or older.

Table SIV.17: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients	There are limited or no data on the clinical safety and efficacy of Nerlynx when administered to patients with significantly impaired hepatic function. Section 4.3 of the SmPC indicates that severe hepatic impairment (Child Pugh C) is contraindicated. Renal impairment is unlikely to affect the PK of Nerlynx given that the percentage of neratinib excreted in the urine is less than 0.5%. Non-clinical and clinical studies did not indicate cardiotoxic properties of neratinib. There are limited or no data on the clinical safety and efficacy of Nerlynx when administered to patients with clinically significant or uncontrolled cardiac disease. There are no data on immunocompromised patients.
Patients with active CNS malignancies or secondary malignancies	Patients with brain metastases are routinely excluded from clinical trials testing new anticancer agents, due to poor ECOG status, prognosis, life expectancy, or lack of intact blood-brain barrier. Patients with secondary malignancies were excluded from clinical studies to reduce confounding effects.
Population with relevant different ethnic origin	In the ExteNET trial, most patients were White (1,156 patients); 188 patients were Asian; 25 were Black or African American; and 39 were of Other ethnic/racial origin.
Subpopulations carrying relevant genetic polymorphisms	Genome-wide association studies did not find any increased risk of BC in the presence of ERBB2 SNP (Han et al, 2005; Benusiglio et al, 2005; Benusiglio et al, 2006; Breyer et al, 2009). Given the negative results from these previous studies, the possibility of identifying a pathogenic germline variant with a relevant population frequency is unlikely.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

The US FDA approved Nerlynx for the extended adjuvant treatment of adult patients with early-stage HER2 overexpressed/amplified BC, following adjuvant trastuzumab-based therapy on 17 July 2017. Nerlynx was also approved in combination with capecitabine, for the treatment of adult patients with

advanced or metastatic HER2+ BC who have received two or more prior anti-HER2-based regimens in the metastatic setting in the USA on 25 February 2020.

Since the approval of Nerlynx in the USA (July 2017), European Union (EU) (September 2018), Australia (18 March 2019), and Canada (16 July 2019), the following post-authorisation cumulative exposure data have been calculated based on the number of patients who received Nerlynx as of 01 May 2020.

As of 01-May-2020, Nerlynx has been marketed in UK (07 October 2019), Germany (02 December 2019), Hong Kong (22 October 2019), Austria (23 December 2019), China (27 April 2020), Chile (28 April 2020), and in the USA. It is also available for early expanded access in Argentina, Australia, Canada, the EU, South Africa and Singapore.

SV.1.1 Method used to calculate exposure

The post-authorisation cumulative exposure data were calculated based on the number of patients who received Nerlynx as of 01 May 2020.

SV.1.2 Exposure

As of 01 May 2020, an estimated total of 8,437 patients have received treatment with Nerlynx in the post-authorisation setting.

Table SV.18 presents the exposure data by age group, gender, and cumulative dose per day where Nerlynx is currently approved.

Table SV.18: Cumulative data on patients exposed post-authorisation[a]

		Female	Male	Unknown	Total persons
Number of patients exposed by age group					
Age group	<65 years	5,257	54	18	5,329
	>65 years	1,135	22	6	1,163
	Unknown	924	12	1,009	1,945
	Total	7,316	88	1,033	8,437
Number of patients with cumulative dose per day[b]					
Dose [mg/day]	240	-	-	-	5,766
	200	-	-	-	107
	160	-	-	-	129
	120	-	-	-	102
	80	-	-	-	13
	Other	-	-	-	2,320
	Total	-	-	-	8,437

[a]Estimated total of number patients who received Nerlynx in countries where it is approved for commercial use and for compassionate use on a per-patient basis.
[b]Liquid Hub data through 01 May 2020.
Calculated by taking average of Quantity Shipped/Day supply.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Nerlynx is a prescription-only medicinal product that should be prescribed by an experienced physician. No effects that would trigger abuse for illegal purpose have been identified for Nerlynx. The potential for misuse for illegal purpose is very limited.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Clinical development programmes are restricted to the enrolled study population eligible under the protocol specified inclusion and exclusion criteria. The following information outlines limitations of the programme in generalising the safety observations of the Phase 2/3 studies with Nerlynx to the patients in the expected target indication.

Table SVII.19: Limitation of adverse drug reaction detection common to clinical study development programmes

Ability to detect adverse reactions	Limitation of study programme	Discussion of implications for target population
Due to rare occurrence	Rare ADRs may not have been detected in clinical studies due to limited exposure.	Routine pharmacovigilance surveillance will be in place to detect rare ADRs.
Due to prolonged exposure longer than was studied in the clinical studies	A total of 665 patients received treatment for 12 or more months in the All Clinical Study Population (Part II, Module SIII).	Routine pharmacovigilance activities and signal detection will allow the identification of reactions that may not have been detected in clinical studies.
Due to cumulative effects	Not applicable: Nerlynx has a half-life of about 11 to 14 hours. Therefore, no cumulative effects are expected.	Not applicable.
Due to long latency period	Not applicable.	Not applicable.

Abbreviations: ADR = adverse drug reaction.

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

The important identified risks and important potential risks are based on the non-clinical and clinical trial experience.

The Medical Dictionary for Regulatory Activities (MedDRA) version used and search criteria for these risks, including the applicable Standardised MedDRA Queries (SMQs) and the Preferred Terms (PTs) were used.

Important identified risks with the use of Nerlynx are:

- Gastrointestinal toxicity – diarrhoea and stomatitis
- Hepatotoxicity

Important potential risks that may be associated with the use of Nerlynx are:

- Cardiotoxicity – left ventricular ejection fraction (LVEF) decreased

- Pulmonary toxicity – interstitial lung disease (ILD)
- Reproductive and developmental toxicity

The following tables present the proportion of patients with relevant events from the following studies:

- Randomised, blinded study:
  - 3144A2-3004-WW / B1891004 (ExteNET Study)
- Other studies:
  - 3144A1-201-WW / B1891012
  - 3144A2-3003-WW / B1891003
  - PUMA-NER-6201

The clinical study data are presented using MedDRA version 17.0.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks and important potential risks, and missing information

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

SVII.3.1.1. Important identified risks

SVII.3.1.1.1. Important identified risk – Gastrointestinal toxicity (diarrhoea)

Search method: SMQ level 1: *Non-infectious diarrhoea* (narrow and broad search)

The incidence, relative risk, outcome, and severity of diarrhoea are presented for monotherapy with neratinib in Table SVII.20.

Table SVII.20: Important identified risk (neratinib monotherapy) – Gastrointestinal toxicity (diarrhoea)

SMQ: Non-infectious diarrhoea (broad and narrow search)

	Randomised, blinded monotherapy breast cancer (ExteNET Study)			All monotherapy breast cancer studies
	Neratinib (N=1,408)		Placebo (N=1,408)	Neratinib (N=1,710)
Incidence[a] n (%)	1,345 (95.5)		512 (36.4)	1,603 (93.7)
Relative risk[b]		2.627		
(95% confidence interval)		(2.449, 2.817)		
Incidence of serious events	23 (1.6)		4 (0.3)	35 (2.0)
Outcome[c]				
Resulted in death	0 (0.0)		0 (0.0)	0 (0.0)

	Randomised, blinded monotherapy breast cancer (ExteNET Study)			All monotherapy breast cancer studies
	Neratinib (N=1,408)		Placebo (N=1,408)	Neratinib (N=1,710)
Recovered	1,278 (90.8)		495 (35.2)	1,492 (87.3)
Did not recover	67 (4.8)		17 (1.2)	111 (6.5)
Missing	0 (0.0)		0 (0.0)	0 (0.0)
Severity[d]				
Worst grade=1	324 (23.0)		387 (27.5)	418 (24.4)
Worst grade=2	457 (32.5)		101 (7.2)	547 (32.0)
Worst grade=3	563 (40.0)		24 (1.7)	634 (37.1)
Worst grade=4	1 (0.1)		0 (0.0)	4 (0.2)
Worst grade=5	0 (0.0)		0 (0.0)	0 (0.0)
Missing grade	0 (0.0)		0 (0.0)	0 (0.0)

[a] All patients with at least one adverse event.
[b] Active versus Placebo.
[c] A patient with multiple events is counted once using the outcome of the last event.
[d] Grade was based on CTCAE V3.0 or above.
All Monotherapy breast cancer includes studies: 3144A1-201-WW, 3144A2-3003-WW, 3144A2-3004-WW, and PUMA-NER-6201
Program: Y:\stat\neratinib\meta\nda_ebc\iss\csr\program\rmp\t-rmp-eoi-sum.sas
Output: t02-01-01-eoi-gi-diarrhea-broad-bc.rtf (Date Generated: 19JAN2016:17:01) Source: adae, adsl

Nature of the risk:

Clinical Trial with Monotherapy (ExteNET Trial)

During the ExteNET trial, where prophylaxis with loperamide was not mandatory, 95.5% of Nerlynx-treated adult patients with early-stage HER2-overexpressed/amplified BC who have received prior adjuvant trastuzumab-based therapy experienced diarrhoea (all grades), versus 36.4% in the placebo arm. Serious diarrhoea was reported in 1.6% of patients in the Nerlynx arm versus 0.3% in the placebo arm. The proportion of patients with diarrhoea of grade 3 was 40.0% in the Nerlynx arm and 1.7% in the placebo arm. There was one non-serious case of grade 4 diarrhoea (0.1%) in the Nerlynx arm. Diarrhoea led to hospitalisation in 1.4% of Nerlynx-treated patients.

Interim results (data cut-off date: 03 April 2020) from the CONTROL trial (PUMA-NER-6201), an international, open label, Phase 2 trial investigating the use of antidiarrheal prophylaxis or dose escalation in the reduction of neratinib associated diarrhoea that had a primary endpoint of the incidence of grade 3 diarrhoea. The interim analysis included a total of 501 patients listed by cohorts below:

- 137 patients who received neratinib plus loperamide prophylaxis,
- 64 patients who received neratinib plus loperamide prophylaxis for 2 cycles and budesonide for 1 cycle,
- 136 patients who received neratinib plus loperamide prophylaxis for 1 cycle and colestipol for 1 cycle,
- 104 patients who received colestipol for 1 cycle and loperamide as needed, and
- 60 patients who received the dose escalation regimen of neratinib.

The results of the trial showed that the incidence of grade 3 diarrhoea for the 137 patients who received the loperamide prophylaxis was 30.7% and that for the 137 patients in this cohort, 20.4%

discontinued neratinib due to diarrhoea. The median cumulative duration of grade 3 diarrhoea was three days.

For the 64 patients who received the combination of loperamide plus budesonide, the incidence of grade 3 diarrhoea was 28.1% and for the 64 patients in this cohort, 10.9% discontinued neratinib due to diarrhoea. The median cumulative duration of grade 3 diarrhoea was three days.

For the 136 patients who received the combination of loperamide plus colestipol, the incidence of grade 3 diarrhoea was 20.6% and for the 136 patients in this cohort, 3.7% discontinued neratinib due to diarrhoea. The median cumulative duration of grade 3 diarrhoea was three and a half days.

For the 104 patients who received colestipol and loperamide as needed, the incidence of grade 3 diarrhoea was 31.7% and for the 104 patients in this cohort, 7.7% discontinued neratinib due to diarrhoea. The median cumulative duration of grade 3 diarrhoea was two days.

For the 60 patients who received no antidiarrheal drugs as mandatory prophylaxis and dose escalation of neratinib in the first month, the incidence of grade 3 diarrhoea was 13.3% and that for the 60 patients in this cohort, 3.3% discontinued neratinib due to diarrhoea. The median cumulative duration of grade 3 diarrhoea was two and a half days.

As of the data cutoff date, there were no cases of Grade 4 or Grade 5 diarrhea reported among total 501 patients who completed their due course of treatment irrespective of their cohorts. The median cumulative duration of grade 3 or higher diarrhoea spanned 2 to 4 days across regimens for the entire treatment period.

All prophylactic regimens reduced the incidence of grade 3 diarrhoea and drug discontinuation compared with the prior ExteNET trial. The dose escalation cohort demonstrated a clear benefit in avoiding some other gastrointestinal toxicities such as nausea, vomiting, and constipation, likely side effects of the required antidiarrheals of the other cohorts. It had the lowest incidences of these toxicities as compared to the other cohorts. In addition, it had the lowest rate of early treatment discontinuation due to diarrhea. allowing more patients to receive the benefit of the full year of neratinib treatment.

In summary, dose escalation improves the management of neratinib associated diarrhea by reducing the incidence of Grade 3 diarrhea and offers an alternative to the current dosing regimen. (CONTROL Interim CSR, 12 August 2020)

All Clinical Study Population

Cumulatively as of 01 May 2020, there were 4,868 AEs (157 serious) pertaining to the identified risk of diarrhoea in the clinical trials setting. The 4,868 AEs of diarrhoea occurred in a total patient population of 6,605, resulting in an incidence rate of 74.0%.

A total of 2,732 AEs of diarrhoea occurred in 2,684 patients on neratinib monotherapy (n=2,777), resulting in an incidence rate of 96.7%. Of these 2,684 patients, four had grade 4 events (0.14%), 902 had grade 3 events (33.0%), and the remaining patients had either grade 1 (33.0%) or grade 2 (33.0%); no grade 5 events were reported. Of the 2,684 patients who had diarrhoea, 62 had an SAE of diarrhoea. Fifty-three out of 62 patients were hospitalised for the event, seven patients had important medical events of diarrhoea, and one patient had significant disability. Fifty-nine of the 62 patients recovered after treatment. The outcome in two patients was not known at the time of the last follow-up and one patient recovered with sequelae. The four grade 4 events of diarrhoea occurred in patients who participated in studies where diarrhoea management with antidiarrheal prophylaxis was not mandatory. One patient who participated in the pivotal trial ExteNET, experienced a grade 4 event but was not hospitalised; the event resolved after treatment. Three of

the four patients who were hospitalised recovered with treatment and temporary interruption or discontinuation of study drug. Of the 2,684 patients who had diarrhoea, 242 patients had dose reduction and 230 patients had study-drug discontinuation. The outcome of the events of diarrhoea were reported as recovered in 2,462 patients (90.0%), recovered with sequelae in 12 patients (0.4%), recovering at the time of the report in six patients (0.2%), not recovered in 213 patients (7.8%), and unknown in three patients (0.1%) at the time of the last follow-up.

A total of 1,222 events of diarrhoea occurred in 1,183 patients on neratinib combination therapy (n=1,301), resulting in an incidence rate of 91.0%; 366 (28.0%) in patients on neratinib plus capecitabine combination (N+C), 24 (1.9%) in patients on neratinib plus digoxin (N+D), 41 (3.2%) in patients on neratinib plus fulvestrant (N+F), 38 (2.9%) in patients on neratinib plus fulvestrant plus trastuzumab (N+F+T), 360 (28%) in neratinib plus paclitaxel (N+P), 110 (8.5%) in patients on neratinib plus trastuzumab (N+T), 185 (14.0%) in patients on neratinib plus temsirolimus (N+TS), and 98 (7.5%) in patients on neratinib plus vinorelbine (N+V). Of these 1,183 patients, one patient had a grade 5 event, two had grade 4 events, 1,065 had grade 3 events, and the remaining patients had grade 1 or 2 events. A total of 73 patients had an SAE of diarrhoea: 25 patients on N+C, 23 on N+P, 12 on N+T, 10 on N+TS, two on N+V, and one on N+F+T. Sixty-seven patients were hospitalised and six had important medical events of diarrhoea. The grade 5 event was downgraded by the investigator as a grade 3 since the patient died due to disease progression while on treatment with N+T for BC in the SUMMIT trial (2019IL007731). The two cases of grade 4 diarrhoea in patients on neratinib combination, N+P (2018US009139) and N+C (2009ES000597), had outcomes of recovered and resumed study treatment. The outcome of the SAE of diarrhoea was recovered in 65 patients, recovered with sequelae in two patients, and not recovered at the time of the last follow-up in six patients. Of the 1,222 AEs of diarrhoea, 61 events led to dose reduction and 24 events led to permanent discontinuation of neratinib. Outcome of the event was reported as recovered in 804 (62.0%) patients, recovering at the time of the report in 8 (0.6%) patients, recovered with sequelae in 13 (1.0%) patients, and not recovered in 162 (13.0%) patients.

A total of 531 events of diarrhoea that occurred in 512 patients on placebo (n=1,424), resulting in an incidence rate of 36.0%.

A cumulative review of these events did not identify a new safety finding or change the characteristic of this risk.

Post-authorisation

Cumulatively as of 01 May 2020, a total of 4,370 AEs (259 serious) of diarrhoea in 4,325 patients have been received in the post-authorisation setting, resulting in a reporting rate of 0.999 per patient-year. Preferred Terms retrieved by the SMQ included diarrhoea (n=4,311 [247 serious]), faeces discoloured (n=14), diarrhoea haemorrhagic (n=11 [6 serious]), anal incontinence (n=8 [1 serious]), colitis (n=7 [5 serious]), irritable bowel syndrome (n=3), abnormal faeces (n=3), bowel movement irregularity (n=3), defaecation urgency (n=2), gastrointestinal inflammation (n=2), and one AE each of enteritis, faecal volume increased, frequent bowel movements, gastroenteritis, gastrointestinal motility disorder, and gastrointestinal toxicity.

No fatal AE of diarrhoea has been reported. Of the 4,370 post-authorisation AEs reported, 632 (14.5%) had severity reported. A total of 103 (2.3%) were reported as grade 1 or mild; 32 (0.7%) were reported as grade 2 or moderate; 494 (11.3%) were reported as grade 3 or severe; and 3 (0.07%) were reported as grade 4. Among the total 497 grade 3/severe and grade 4 AEs reported, 410 grade 3 and one grade 4 were reported as non-serious AEs. Of the 4,370 AEs, 1,580 (36.2%) were not resolved, 1,337 (30.6%) were not reported/unknown, 787 (18.0%) were resolving, 663 (15.2%) were resolved, and 3 (0.1%) were resolved with unspecified sequalae.

For case-level action taken with Nerlynx for all 4,370 AEs, the dose was unchanged or not applicable for most patients (n=1,759; 40.1%). Nerlynx was discontinued in 1,092 cases (25.0%), temporarily withheld in 765 cases (17.5%), decreased/reduced in 392 cases (9.0%). In the remaining cases, a dose change was not reported/unknown/blank (n=256; 5.9%), or the patient had a dose increase (n=106; 2.4%), such as drug titration ordered by the prescribing Healthcare Professional (HCP) or an increase in dose following resolution of an AE.

A cumulative review of the PTs retrieved for this risk did not identify any new safety findings or change in the characteristic of this risk.

Background incidence/prevalence:

Diarrhoea is an AE frequently reported in cancer patients, due to a variety of causes and following cancer treatment (Cherny, 2008).

Risk groups and risk factors:

For diarrhoea in general, groups at risk include patients with significant chronic active inflammatory bowel disease or recent acute GI disorder with diarrhoea as a major symptom (e.g., \ Crohn's disease, ulcerative colitis, malabsorption, or grade ≥2 diarrhoea of any aetiology prior to treatment). Aggravating risk factors include concomitant medications and other predisposing conditions including advanced age.

For diarrhoea during treatment with TKIs, a small number of emerging clinical investigations have found an association between drug steady-state concentrations and diarrhoea, suggesting that gene variants within metabolic pathways for TKIs could play a role in toxicity susceptibility (Bowen, 2013).

Potential mechanisms:

Diarrhoea during treatment with TKIs may be due to direct mechanisms caused by the agents themselves, or amplification of injury mechanisms in combination with other cancer agents including chemotherapy and radiotherapy. In the instance of TKI monotherapy, studies have shown that PK of TKIs are not usually associated with diarrhoea, suggesting GI toxicity is predominantly luminal in origin.

The EGFR is expressed by cells of epithelial origin, including the skin and GI tract. The main hypothesis is that inhibition of EGFR signalling will lead to reduced growth and healing of the intestinal epithelium. This in turn leads to mucosal atrophy, due to the stimulatory effect of the EGFR pathway on enterocyte proliferation, nutrient and electrolyte transport, brush boarder enzyme expression, and epithelial restitution being impeded.

Another hypothesis is that diarrhoea may be due to excess chloride secretion caused by dysregulated EGFR signalling to downstream pathways and channels. This has been postulated due to the known inhibitory effects of the EGF on chloride secretion in the intestine and the understanding of the profound influence of chloride in secretory diarrhoea (Bowen, 2013; Van Sebille et al, 2015).

Preventability:

Diarrhoea during Nerlynx treatment can be managed by dose modification and prophylactic treatment with loperamide. The SmPC Sections 4.2 and 4.4 describe the use of antidiarrheal medication, dietary changes, and appropriate dose modifications of Nerlynx in the setting of diarrhoea. In SmPC Section 4.2, antidiarrheal prophylactic treatment with an antidiarrheal medication is recommended during the first two cycles (56 days) of treatment, which should be initiated along with the first dose of Nerlynx. Nerlynx dose interruptions and dose reductions may also be required to manage diarrhoea, for which guidelines are provided in SmPC Section 4.2.

Routine risk minimisation measures for diarrhoea are described in Part V.1., and additional risk minimisation measures are described in Part V.2.

The most recently published interim data from the CONTROL trial (data cut-off date: 03 April 2020) suggested that a rationally-structured regimen of loperamide prophylaxis for one to two cycles reduces the incidence, severity, and duration of neratinib-associated diarrhoea compared with that observed in the ExteNET trial. The addition of budesonide or colestipol to loperamide reduced the rate of neratinib discontinuation due to diarrhoea, allowing patients to receive the efficacy benefits of one year of extended adjuvant therapy. The most recent interim analysis included 60 patients who received the dose-escalation regimen of neratinib (120 mg Week 1, 160 mg Week 2, 240 mg Week 3), and loperamide as needed. For the 60 patients who received no antidiarrheal drugs as mandatory prophylaxis and dose escalation of neratinib in the first month, the incidence of grade 3 diarrhoea was 13.3% and that for the 60 patients in this cohort, 3.3% discontinued neratinib due to diarrhoea. The median cumulative duration of grade 3 diarrhoea was two and a half days.

Neratinib tolerability was improved with pre-emptive prophylaxis or dose escalation which reduced the rate, severity, and duration of neratinib-associated grade ≥3 diarrhoea compared with ExteNET. Lower diarrhoea-related treatment discontinuations in multiple cohorts indicate that proactive management can allow patients to stay on neratinib for the recommended time period (Barcenas et al, 2020).

Overall, the results are comparable to what was observed in Study 3004, where a loss of Quality of Life (QoL) occurred early after neratinib treatment with subsequent recovery.

Evaluation of the impact on QoL of a higher premature discontinuation rate in the loperamide cohort using the last observation carried forward sensitivity analysis demonstrated similar results and did not alter the conclusions.

Impact on individual patient:

Diarrhoea in general can significantly decrease the QoL of patients. Severe diarrhoea can be debilitating and, at times, even life threatening. It contributes to dehydration, electrolyte imbalance, malnutrition, declining immune function, and pressure ulcer formation (Cherny, 2008).

Potential public health impact of safety concern:

Although the incidence of diarrhoea in patients receiving Nerlynx for BC is very common, the severity and duration of Nerlynx-associated diarrhoea can be reduced with prophylactic treatment. However, if recommendations for prophylactic treatment and dose modification are not followed, this could result in hospitalisation due to diarrhoea.

Considering the usage of Nerlynx in the general population is not wide (i.e., only in adult patients with early-stage HER2-overexpressed/amplified BC, representing 4 to 19/100,000 cases; Ferlay et al, 2013, Wolff et al, 2013) and it is not expected to have significant off-label use, the impact on public health is expected to be low. Distribution of educational material should contribute to patient-adherence of prophylactic treatment.

Evidence source:

Non-clinical, clinical, and post-authorisation experience with neratinib treatment.

SVII.3.1.1.2. Important identified risk – Gastrointestinal toxicity (stomatitis)

Search Method: Since there is no MedDRA SMQ for stomatitis, the event term was defined using the following MedDRA PTs - aphthous ulcer, cheilitis. glossitis, glossodynia, mouth ulcerations, mucosal inflammation, oral mucosal blistering, oral pain, oropharyngeal pain, stomatitis

The incidence, relative risk, outcome, and severity of stomatitis are presented for monotherapy with neratinib in Table SVII.21.

Table SVII.21: Important identified risk (neratinib monotherapy) – Gastrointestinal toxicity (stomatitis)

	Randomised, blinded monotherapy breast cancer (ExteNET trial)			All monotherapy breast cancer studies
	Neratinib (N=1,408)		Placebo (N=1,408)	Neratinib (N=1,710)
Incidence[a] n (%)	152 (10.8)		45 (3.2)	192 (11.2)
Relative risk[b]		3.378		
(95% confidence interval)		(2.442, 4.672)		
Incidence of serious events	0 (0.0)		0 (0.0)	1 (0.1)
Outcome[c]				
Resulted in death	0 (0.0)		0 (0.0)	0 (0.0)
Recovered	129 (9.2)		41 (2.9)	164 (9.6)
Did not recover	23 (1.6)		4 (0.3)	28 (1.6)
Missing	0 (0.0)		0 (0.0)	0 (0.0)
Severity[d]				
Worst grade=1	105 (7.5)		36 (2.6)	136 (8.0)
Worst grade=2	39 (2.8)		8 (0.6)	46 (2.7)
Worst grade=3	8 (0.6)		1 (0.1)	10 (0.6)
Worst grade=4	0 (0.0)		0 (0.0)	0 (0.0)
Worst grade=5	0 (0.0)		0 (0.0)	0 (0.0)
Missing grade	0 (0.0)		0 (0.0)	0 (0.0)

[a] All patients with at least one adverse event.
[b] Active versus Placebo.
[c] A patient with multiple events is counted once using the outcome of the last event.
[d] Grade was based on CTCAE V3.0 or above.
Note: Sponsor-defined search strategy for stomatitis: MedDRA PT aphthous stomatitis, mouth ulceration, mucosal erosion, mucosal inflammation, mucosal ulceration, oral mucosal erosion, oral mucosal blistering, oral mucosal lesion, stomatitis. Stomatitis is a sponsor-defined search strategy, and there is no broad and narrow difference.
All Monotherapy breast cancer includes studies: 3144A1-201-WW, 3144A2-3003-WW, 3144A2-3004-WW, and PUMA-NER-6201
Program: Y:\stat\neratinib\meta\nda_ebc\iss\csr\program\rmp\t-rmp-eoi-sum.sas
Output: t02-01-02-eoi-gi-stomatitis-bc.rtf (Date Generated: 19JAN2016:17:01) Source: adae, adsl

Nature of the risk:

Clinical Trial with Monotherapy (ExteNET Trial)

During the ExteNET trial, 10.8% of Nerlynx-treated patients experienced stomatitis (all grades), versus 3.2% in the placebo arm. The proportion of patients with stomatitis of grade 3 was 0.6% in the Nerlynx arm and 0.1% in the placebo arm. No serious or grade 4 cases were reported.

All Clinical Study Population

Cumulatively as of 01 May 2020, there were 1,321 AEs (7 serious) pertaining to the identified risk of stomatitis in the clinical trials setting. The 1,321 AEs pertaining to stomatitis occurred in a total patient population of 6,605, resulting in an incidence rate of 20.0%.

A total of 407 AEs of stomatitis occurred in 362 patients on neratinib monotherapy (n=2,777), resulting in an incidence rate of 13.0%. Of these 362 patients, 12 had grade 3, and the remaining

patients had grade 1 or 2 events; no grade 4 or grade 5 events were reported. There were four patients with events that led to dose reductions and five patients with events that led to permanent discontinuation of neratinib. The outcome of the event was recovered in 347 (13.0%) patients, recovering in 1 (0.036%) patient, not recovered in 58 (2.1%) patients, and unknown in 1 (0.04%) patient. There was one serious case of stomatitis in a 47-year-old female patient who developed grade 3 stomatitis with grade 3 leucocytosis, grade 3 gastroenteritis, and grade 3 hypokalaemia about three months after receiving neratinib as study treatment for BC in the CONTROL trial (2015US005029). The case was confounded by radiation therapy and concurrent diabetes mellitus.

A total of 551 events of stomatitis occurred in 456 patients on neratinib combination therapy (n=1,301), resulting in an incidence rate of 35.0%; 142 (11%) in patients on N+C, 5 (0.38%) in N+F, 5 (0.38%) in N+F+T, 150 (12.0%) in N+P, 19 (1.5%) in N+T, 183 (14.0%) in N+TS, and 47 (3.6%) in N+V. Of these 456 patients, 37 had grade 3 events, and the remaining patients had grade 1 or grade 2 events; no grade 4 or grade 5 events were reported. There were four patients with events that led to dose reductions and five patients with events that led to permanent discontinuation of neratinib. The outcome was reported as recovered in 292 (22.0%) patients, recovering in 13 (1.0%) patients, recovered with sequelae in 4 (0.3%) patients, persisted in 18 (1.4%) patients, not recovered in 145 (11.0%) patients, and unknown in one patient (0.08%). There were four patients who had SAEs, three with stomatitis and one with mucosal inflammation. One patient had a grade 3 event of stomatitis and the remaining patients had grade 3 events. Three of the patients were on treatment with N+TS and one was on treatment with N+C. All four patients recovered after treatment.

A total of 95 AEs pertaining to stomatitis occurred in 89 patients on placebo (n=1,424), resulting in an incidence rate of 6.3%.

A cumulative review of these events did not identify a new safety finding or change the characteristic of this risk.

Post-authorisation

Cumulatively as of 01 May 2020, a total of 231 AEs (8 serious) of stomatitis in 228 patients have been received in the post-authorisation setting, resulting in a reporting rate of 0.053 per patient-year. Preferred Terms retrieved by the company-defined search strategy included stomatitis (n=214 [8 serious]), mouth ulceration (n=8), oral mucosal blistering (n=8), and mucosal inflammation (n=1).

No fatal AE of stomatitis has been reported. Of the 231 AEs, 7 (3.0%) had severity reported. Three (1.3%) were reported as mild; 4 (1.7%) were reported as grade 3 or severe although all these grade 3 AEs were non-serious. Of the 231 AEs, 41 (17.7%) were not resolved, 131 (56.7%) were not reported/unknown, 31 (14.4%) were resolved, and 28 (12.1%) were resolving.

For case-level action taken with Nerlynx, the dose was not changed/not applicable in 85 cases (36.8%), temporarily withdrawn in 55 cases (23.8%), discontinued in 53 cases (22.9%), reduced/decreased in 26 cases (1.2%), not reported/unknown in 10 cases (4.3%), and was increased in two cases (0.9%).

A cumulative review of these PTs retrieved for this risk did not identify any new safety findings or change the characteristic of this risk.

<u>Background incidence/prevalence:</u>

During the ExteNET trial, stomatitis was reported by 3.2% of placebo-treated adult patients with early-stage HER2-overexpressed/amplified BC who have received prior adjuvant trastuzumab-based therapy.

Risk groups and risk factors:

Among patient-related risk factors, comorbidities such as malnutrition and poor oral health can contribute relevantly to the risk of oral mucositis (stomatitis) (Seiler et al, 2014).

Potential mechanisms:

Although the clinical symptoms of mucositis are largely the result of epithelial injury, the condition itself is the consequence of a dynamic series of biological events that take place throughout the different cellular and tissue compartments of the mucosa. Cytotoxic treatment affects the epithelium as well as all other tissues and cells of the mucosa. The model of the pathogenesis of mucositis developed by Sonis et al (2004) suggests a process divided into 5 phases: initiation, upregulation with generation of messenger signals, signalling and amplification, ulceration, and healing. To date, it is unproven whether the pathogenesis of mucositis observed in patients receiving new molecular targeted therapies is comparable with that of mucositis caused by conventional cancer therapies and radiation (Seiler et al, 2014). Mucositis caused by targeted therapies differs among other things in appearance, course, concomitant AEs, and toxicity, and thus could be perceived as an entity distinct from conventional mucositis with its own pathogenic mechanisms. Some authors strongly believe that immune mechanisms are involved in this process, but further research is needed (Seiler et al, 2014).

Increased tyrosine phosphorylation of proteins is necessary for physiological and pathologic regeneration. Regeneration of the gastric mucosa following a wound or an injury is controlled by a number of growth factors (such as EGF, platelet-derived growth factor and hepatocyte growth factor), which coordinate proliferation and migration of cells after binding to specific receptors on the cell surface. During ulcer healing, proto-oncogene tyrosine-protein kinase is activated by the EGF cascade and regulates cell migration. Animal studies have shown significantly increased phosphorylation of EGFR after ulcer induction and an increase in EGFR expression in the early stages of ulcer healing, localised in the epithelial cells of the ulcer margins and regenerating glands (Shah et al, 2014).

Preventability:

All patients regardless of age as well as caregivers and family members should be well informed about the risk of stomatitis as a possible consequence of the planned therapy. Proper education on the importance of optimal oral hygiene including careful brushing with a soft bristle toothbrush, flossing, and non-medicated alcohol-free mouth rinses with, e.g., saline or sodium bicarbonate several times a day are key elements. Due to its antiplaque and antimicrobial effects, chlorhexidine may be considered as part of basic oral care. Exogenous noxae such as tobacco, alcohol, and spicy, acidic, or very hot food should be avoided during treatment. In addition, a dental examination before initiation and during cancer treatment is recommended as well as regular dental prophylaxis and treatment whenever indicated (Seiler et al, 2014).

Routine risk minimisation measures for stomatitis are described in Part V.1., and additional risk minimisation measures are described in Part V.2.

Impact on individual patient:

Mucositis/stomatitis is often associated with intense pain impacting nutrition, QoL, and treatment adherence. Damage to the oral mucosa and reduced immunity due to cancer therapy make patients prone to opportunistic infections such as oral candidiasis and herpes simplex infection (Seiler et al, 2014).

Potential public health impact of safety concern:

Although, stomatitis may be associated with intense pain affecting nutrition and QoL, the majority of the stomatitis events reported by Nerlynx-treated patients were grade 1 or 2; with only 0.6% of patients reporting grade 3 events.

Overall, the impact of stomatitis due to Nerlynx on public health is considered to be low.

Evidence source:

Non-clinical, clinical, and post-authorisation experience with neratinib treatment.

SVII.3.1.1.3. Important identified risk – Hepatotoxicity (general)

Search methods: MedDRA SMQs *Biliary Disorders* and *Hepatic Disorders*

SMQ level 1: *Biliary disorders*
- SMQ level 2: *Functional, inflammatory and gallstone related biliary disorders*
  - SMQ level 3: *Biliary system related investigations, signs and symptoms* (narrow search)

SMQ level 1: *Hepatic disorders*
- SMQ level 2: *Drug related hepatic disorders* - comprehensive search
  - SMQ level 3: *Liver related investigations, signs and symptoms* (narrow and broad search)
  - SMQ level 3: *Cholestasis and jaundice of hepatic origin* (narrow and broad search)
  - SMQ level 3: *Drug related hepatic disorders* - severe events only
    - SMQ level 4: *Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions* (narrow and broad search)
    - SMQ level 4: *Hepatitis, non-infectious* (narrow and broad search)

The incidence, relative risk, outcome, and severity of general hepatotoxicity are presented for monotherapy with neratinib in Table SVII.22.

Table SVII.22: Important identified risk (neratinib monotherapy) – Hepatotoxicity

	Randomised, blinded monotherapy breast cancer (ExteNET trial)			All monotherapy breast cancer studies
	Neratinib (N=1408)		Placebo (N=1,408)	Neratinib (N=1,710)
Incidence[a] n (%)	174 (12.4)		93 (6.6)	210 (12.3)
Relative risk[b]		1.871		
(95% confidence interval)		(1.471, 2.380)		
Incidence of serious events	4 (0.3)		2 (0.1)	9 (0.5)
Outcome[c]				
Resulted in death	0 (0.0)		0 (0.0)	0 (0.0)
Recovered	139 (9.9)		59 (4.2)	166 (9.7)
Did not recover	35 (2.5)		34 (2.4)	44 (2.6)
Missing	0 (0.0)		0 (0.0)	0 (0.0)

Table SVII.22: Important identified risk (neratinib monotherapy) – Hepatotoxicity

	Randomised, blinded monotherapy breast cancer (ExteNET trial)			All monotherapy breast cancer studies
	Neratinib (N=1408)		Placebo (N=1,408)	Neratinib (N=1,710)
Severity[d]				
Worst grade=1	84 (6.0)		62 (4.4)	93 (5.4)
Worst grade=2	65 (4.6)		23 (1.6)	76 (4.4)
Worst grade=3	22 (1.6)		7 (0.5)	37 (2.2)
Worst grade=4	3 (0.2)		1 (0.1)	4 (0.2)
Worst grade=5	0 (0.0)		0 (0.0)	0 (0.0)
Missing grade	0 (0.0)		0 (0.0)	0 (0.0)

[a] All patients with at least one adverse event.
[b] Active versus Placebo.
[c] A patient with multiple events is counted once using the outcome of the last event.
[d] Grade was based on CTCAE V3.0 or above.
All Monotherapy breast cancer includes studies: 3144A1-201-WW, 3144A2-3003-WW, 3144A2-3004-WW, and PUMA-NER-6201
Program: Y:\stat\neratinib\meta\nda_ebc\iss\csr\program\rmp\t-rmp-eoi-sum.sas
Output: t02-01-03-eoi-hepat-bc.rtf (Date Generated: 19JAN2016:17:01) Source: adae, adsl

Nature of the risk:

Clinical Trial with Monotherapy (ExteNET Trial)

In the ExteNET trial, liver-associated adverse reactions were reported more frequently in the Nerlynx arm compared with the placebo arm (12.4% vs 6.6%), due primarily to adverse reactions of ALT increased (8.5% vs 3.2%), AST increased (7.4% vs 3.3%) and blood ALP increased (2.1% vs 1.1%). grade 3 and 4 adverse reactions were reported in 1.8% vs 0.6% of Nerlynx- and placebo-treated patients, respectively. Grade 3 and 4 ALT increased was reported in 1.3% vs 0.2%, and AST increased was reported in 0.7% vs 0.3% of Nerlynx vs placebo-treated patients. All were reversible upon treatment discontinuation or interruption.

In the ExteNET trial, laboratory findings of AST (27.6% vs 19.7%) and ALT (37.8% vs 24.8%) elevation were experienced by more Nerlynx-treated than placebo-treated patients, were mostly grade 1 or 2 elevations, and generally occurred early in the course of treatment, as evidenced by an increase in mean levels at Day 7, which decreased to baseline by Month 1. Liver aminotransferase (AT) elevations were reversible either spontaneously without dose change, with dose reduction, or with dose discontinuation. There was a higher frequency of modest AT elevation in the Nerlynx arm than the placebo arm and, although number are small, there were higher numbers of patients with higher order elevations (>10×ULN and >20×ULN) in the Nerlynx arm than in the placebo arm. Of the patients with higher order AT elevations, none met the definition of drug-induced liver injury (DILI); that is, all patients either experienced negative rechallenge, had an alternative etiologic explanation, or had simultaneous elevation in ALP indicative of cholestasis and not DILI. One patient in each arm showed laboratory abnormalities possibly consistent with Hy's law (i.e., concurrent elevations of ALT and/or AST >3×ULN, bilirubin ≥2×ULN, and ALP <2×ULN on the same day of measurement). The Nerlynx-treated patient was also on tamoxifen, which is a potential alternative explanation, and the placebo-treated patient experienced disease recurrence and was hospitalised with hepatic function abnormal and obstructive jaundice 126 days after starting placebo. An external consultant on DILI/hepatotoxicity independently reviewed the hepatic AEs and laboratory data of the Nerlynx-treated patient and assessed that alternative aetiologies were likely and that this case should not be viewed as a Hy's law case in terms of liver safety implications. The external consultant also reviewed the six cases in the ExteNET trial that met Hy's law criteria. The Expert Report,

included in the original RMP submission, concluded that, while it was clear that neratinib can cause hepatocellular injury in some patients, none of the six cases should be considered Hy's law cases.

All Clinical Study Population

Cumulatively as of 01 May 2020, there were 2,033 AEs (107 serious) pertaining to the identified risk of hepatoxicity in the clinical trials setting. The 2,033 AEs pertaining to hepatotoxicity occurred in a total patient population of 6,605, resulting in an incidence rate of 31.0%.

A total of 777 AEs pertaining to hepatoxicity occurred in 390 patients on neratinib monotherapy (n=2,777), resulting in an incidence rate of 14.0%. Of these 44 events, 15 were grade 4 events, 21 were grade 3, and the rest of the events consisted of grade 1 or grade 2; there were no grade 5 events reported. There were 13 patients with events that led to dose reduction and 47 patients with events that led to permanent discontinuation of neratinib. The outcome of the events was reported as recovered in 286 (10.0%) patients, recovering in 3 (0.1%) patients, recovered with sequelae in 2 (0.07%) patients, not recovered in 136 (4.9%) patients, and unknown at the time of the last follow-up in 5 (0.2%) patients. There were 44 SAEs pertaining to hepatotoxicity in 21 patients on neratinib monotherapy, of which, seven patients experienced ascites, 12 patients had elevated liver enzymes, and one patient each had varices oesophageal and hepatic encephalopathy. Thirteen patients had outcomes of recovered and eight patients had outcomes of not recovered. Of the eight patients with outcomes of not recovered, six patients had ascites, which was likely due to progression of underlying disease. The other two patients with elevated liver enzymes had outcomes of not recovered at the time of the last follow-up visit.

A total of 657 events pertaining to hepatotoxicity occurred in 293 patients on neratinib combination therapy (n=1,301), resulting in an incidence rate of 22.5%; 237 (18.0%) in N+C, 9 (0.7%) in N+F, 12 (0.9%) in N+F+T, 180 (14.0%) in N+P, 52 (4.0%) in N+T, 121 (9.3%) in N+TS, and 45 (3.5%) in N+V. Of these 293 patients, four had grade 5 events, 10 had grade 4 events, 126 had grade 3 events, and the remaining patients had grade 1 or grade 2 events. There were three patients with events that led to dose reduction and 13 patients with events that led to permanent discontinuation of neratinib. The outcome of the events was reported as recovered in 183 (14.0%) patients, recovering in 5 (0.4%) patients, recovered with sequelae in 5 (0.4%) patients, not recovered in 135 (10.0%) patients, unknown at the time of the report in 2 (0.2%) patients, and fatal in 3 (0.2%) patients. There were 36 SAEs in 18 patients on neratinib combination therapy, five patients on N+C, five patients on N+T, four patients on N+P, two patients on N+V, and one patient each on N+F, N+F+T, and N+TS. Two patients in the N+P group and one patient in N+C group had fatal outcomes, likely due to progression of underlying disease since all three patients had advanced-stage disease.

A total of 146 AEs pertaining to hepatotoxicity occurred in 93 patients on placebo (n=1,424), resulting in an incidence rate of 6.5%.

A cumulative review of these events did not identify a new safety finding or change the characteristic of this risk.

Post-authorisation

Cumulatively as of 01 May 2020, a total of 218 AEs (82 serious) related to hepatotoxicity in 198 patients have been received in the post-authorisation setting, resulting in a reporting rate of 0.050 per patient-year. Preferred Terms retrieved for this risk by the SMQs included hepatic enzyme increased (n=86 [29 serious]), liver function test (LFT) increased (n=24 [15 serious]), ALT increased (n=19 [7 serious]), AST increased (n=11 [5 serious]), faeces pale (n=8 [1 serious]), LFT abnormal (n=7), hepatic enzyme abnormal (n=5), hepatic pain (n=5 [1 serious]), ascites (n=4 [all serious]), blood ALP increased (n=4), blood bilirubin increased (n=4 [1 serious]), hepatic function abnormal (n=4 [2 serious]), hepatic steatosis (n=4 [1 serious]), hepatitis (n=4 [all serious]), hepatomegaly (n=4 [1 serious]), hepatotoxicity (n=4 [3 serious]), liver disorder (n=4 [1 serious]), abnormal faeces

(n=3), yellow skin (n=3), hepatic failure (n=2 [all serious]), liver injury (n=2 [1 serious]), transaminases increased (n=2), one AE of LFT decreased, and one SAE each of ammonia increased, biliary cirrhosis, hepatic lesion, and ocular icterus (serious).

One fatal AE of ascites has been reported in a patient receiving off-label treatment for cervical cancer. She died on treatment day (TD) 62 from complications associated with her disease including ascites, worsening abdominal pain, and pleural effusion; it was unknown if an autopsy was performed. To date, four cases of hepatitis (2018US006013; 2018US008985; 2019US008568; 2020US000915) and two cases of hepatic failure (2019US006834; 2019US011210) have been reported. Four of these six total cases were confounded by concomitant use of Tylenol (acetaminophen), Toprol (metoprolol succinate), Prilosec (omeprazole), capecitabine, and tamoxifen; all of which are associated with hepatitis/hepatic failure per their USPIs (hepatitis, n=3: 2018US006013; 2019US008568; 2020US000915, and; hepatic failure, n=1: 2019US011210). The remaining two cases, one each with hepatitis and hepatic failure, had insufficient information reported to allow for a meaningful causality assessment (2018US006834; 2019US008985).

Of the 218 AEs reported, 2 (0.9%) had a severity of grade 1 or mild reported. Of these 218 AEs, 1 (0.5%) was fatal, 115 (52.8%) were not reported/unknown, 44 (20.2%) were resolved, 42 (19.3%) were not resolved, and 16 (7.3%) were resolving.

For case-level action taken with Nerlynx, the drug was temporarily withheld for 69 (31.6%) cases, discontinued in 66 (30.1%) cases, not changed or not applicable in 52 (23.9%) cases, reduced/decreased in 22 (10.1%) cases, not reported/unknown in 6 (2.6%) cases, and increased in 3 (1.4%) cases.

Most post-authorisation cases received were solicited cases; therefore, there are limited lab test results reported. A majority (76.6%) of the reported AEs (n=168 [60 serious]) involved PTs associated with liver impairment/liver function abnormality such as AST/ALT increase, hepatic enzyme increased, hepatic enzyme abnormal, LFTs increased/decreased, LFTs abnormal and transaminases increased, ammonia increased, blood bilirubin increased, and blood alkaline phosphatase increased. One case in which lab tests were reported was for a 40-year-old BC patient who experienced flu-like symptoms with a fever of 101.7°F, nausea, body ache, fatigue, chills, and a rash on TD 45; Nerlynx and all her medications were discontinued (2018US001197). On TD 49, LFTs showed an ALT increase of 703 from 17 (units and reference range not specified) and bilirubin increase of 3.4 from 0.5 (units and reference range not specified) on TD 49 with Nerlynx. She was treated with a taper dose of methylprednisolone for the rash. Rash and elevated ALT and bilirubin were not resolved at the last reporting, but the patient was feeling better. Outcomes for the other events were not reported. The reporting pharmacist assessed the events as related to Nerlynx. The case was confounded by concomitant use of exemestane, which is known to cause hepatitis, ondansetron, which is known to cause elevated LFT results and liver failure, and acetylsalicylic acid, which is known to cause hepatic enzyme elevation and hepatitis, per their respective United States Package Inserts.

A cumulative review of these PTs retrieved for this risk did not identify any new safety findings or change the characteristic of this risk.

Background incidence/prevalence:

Liver-associated adverse reactions were reported in 6.6% of placebo-treated patients enrolled in Nerlynx clinical studies, primarily due to adverse reactions of ALT increased (3.2%), AST increased (3.3%) and blood ALP increased (1.1%).

Risk groups and risk factors:

Risk factors for DILI include increasing age, human immunodeficiency virus /acquired immunodeficiency syndrome infection and antiretroviral drug use, chronic hepatitis B or C infection, obesity, and non-alcoholic fatty liver disease. Patients taking anti-infectives, psychotropics, lipid-lowering agents, herbal and dietary supplements, and nonsteroidal anti-inflammatory drugs are also at risk (Bell et al, 2009).

Severe toxic effects can be increased when TKIs are taken with a CYP3A4 inhibitor (Spraggs et al, 2013; Shah et al, 2013).

Potential mechanisms:

Hepatotoxicity with asymptomatic elevations of transaminases and hyperbilirubinemia are commonly associated with oral TKIs (Cabanillas et al, 2011). TKI-induced liver injury varies in incidence and severity by drug. An understanding of the mechanisms of TKI-induced liver injury is now emerging. Most molecularly targeted cancer agents are metabolised in the liver via the cytochrome pathway. The likely mechanisms of TKI-induced hepatotoxicity include oxidative stress from reactive metabolites, immune injury, disruption of hepatic bile acid transport and resulting mitochondrial dysfunction. This suggests a direct toxic effect (Spraggs et al, 2013; Hardy et al, 2014).

Preventability:

Nerlynx-induced changes in LFTs appeared to be reversible when Nerlynx was stopped.

Potential cases of DILI (potential Hy's law cases) can be detected via routine assessment of LFTs. Periodic liver function testing is recommended during TKI treatment in patients with pre-existing liver disease (Shah et al, 2013).

Concomitant use of inhibitors of the hepatic drug-metabolising enzyme CYP3A4 will increase neratinib exposure and potentially hepatotoxicity as drug is mainly metabolised in liver, therefore concurrent administration of CYP3A4 inhibitors should be avoided.

The SmPC Section 4.2 describes dose modifications for hepatotoxicity, with guidelines for dose modifications of Nerlynx in the event of liver toxicity.

The SmPC Section 4.4 describes that LFTs including ALT, AST, and total bilirubin (TBL) should be monitored at one week, then monthly for the first three months and every six weeks thereafter or as clinically indicated. Patients who experience ≥grade 3 any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, should be evaluated for changes in LFTs. Fractionated bilirubin and prothrombin time should also be collected during hepatotoxicity evaluation.

The SmPC Section 4.3 states that Nerlynx is contraindicated in patients with Child Pugh C hepatic impairment. No dose adjustment is required in patients with Child Pugh A or B (mild to moderate) hepatic impairment (SmPC Section 4.2).

Routine risk minimisation measures for hepatotoxicity are described in Part V.1., and additional risk minimisation measures are described in Part V.2.

Impact on individual patient:

Fatality from TKI-induced hepatotoxicity is uncommon compared with hepatotoxic drugs in other classes but may lead to long-term consequences such as cirrhosis (Shah et al, 2013).

Potential public health impact of safety concern:

Liver-associated adverse reactions in Nerlynx-treated patients are mild to moderate for a majority of cases and reversible upon treatment discontinuation.

Considering the usage of Nerlynx in the general population is not wide (i.e., only in adult patients with early-stage HER2-overexpressed/amplified BC, representing 4 to 19/100,000 cases; Ferlay et al, 2013; Wolff et al, 2013) and there is no significant off-label use, the impact on public health is expected to be low.

Evidence source:

Non-clinical, clinical, and post-authorisation experience with neratinib treatment.

SVII.3.1.2. Important potential risks

SVII.3.1.2.1. Important potential risk – Cardiotoxicity (left ventricular ejection fraction decreased)

Search method: SMQ level 1: *Cardiac failure* (narrow and broad search)

The incidence, relative risk, outcome, and severity of decreased LVEF are presented for monotherapy with neratinib in Table SVII.24.

Table SVII.23: Important potential risk (neratinib monotherapy) – Cardiotoxicity (left ventricular ejection fraction decreased)

SMQ: cardiac failure (broad and narrow search)

	Randomised, blinded monotherapy breast cancer (ExteNET trial)			All monotherapy breast cancer studies
	Neratinib (N=1,408)		Placebo (N=1,408)	Neratinib (N=1,710)
Incidence[a] n (%)	94 (6.7)		119 (8.5)	116 (6.8)
Relative risk[b]		0.790		
(95% confidence interval)		(0.609, 1.025)		
Incidence of serious events	0 (0.0)		1 (0.1)	0 (0.0)
Outcome[c]				
Resulted in death	0 (0.0)		0 (0.0)	0 (0.0)
Recovered	54 (3.8)		83 (5.9)	66 (3.9)
Did not recover	40 (2.8)		36 (2.6)	50 (2.9)
Missing	0 (0.0)		0 (0.0)	0 (0.0)
Severity[d]				
Worst grade=1	66 (4.7)		92 (6.5)	83 (4.9)
Worst grade=2	22 (1.6)		25 (1.8)	27 (1.6)
Worst grade=3	6 (0.4)		2 (0.1)	6 (0.4)
Worst grade=4	0 (0.0)		0 (0.0)	0 (0.0)
Worst grade=5	0 (0.0)		0 (0.0)	0 (0.0)
Missing grade	0 (0.0)		0 (0.0)	0 (0.0)

[a] All patients with at least one adverse event.
[b] Active versus Placebo/comparator.
[c] A patient with multiple events is counted once using the outcome of the last event.
[d] Grade was based on CTCAE V3.0 or above.
All Monotherapy breast cancer includes studies: 3144A1-201-WW, 3144A2-3003-WW, 3144A2-3004-WW, and PUMA-NER-6201
Program: Y:\stat\neratinib\meta\nda_ebc\iss\csr\program\rmp\t-rmp-eoi-sum.sas
Output: t02-01-07-eoi-cardiac-failure-broad-bc.rtf (Date Generated: 18FEB2016:10:24) Source: adae, adsl

Nature of the risk:

In theory, Nerlynx may decrease LVEF as this risk was identified for similar compounds (class effect).

Non-clinical trials and clinical studies did not indicate cardiotoxic properties of Nerlynx.

Clinical Trial with Monotherapy (ExteNET Trial)

During the ExteNET trial, TEAEs associated with the cardiac failure SMQ were reported at similar frequencies in the Nerlynx arm and placebo arm (6.7% and 8.5%, respectively). The incidence of ejection fraction decreased was comparable between the two treatment arms (3.9%, Nerlynx and 3.8%, placebo); the incidence of oedema peripheral was 1.3% in the Nerlynx arm and 2.8% in the placebo arm. Among patients with a post-baseline LVEF assessment measured by echocardiogram (ECHO)/multigated acquisition scan (MUGA), LVEF decrease (absolute decrease of >10% but <50%) occurred in 1.1% of patients, and absolute decrease of ≥15% occurred in 3.4% of patients.

There were 2,549 patients with a post-baseline LVEF assessment: 1,187 patients in the Nerlynx arm and 1,362 in the placebo arm. In the Nerlynx arm, 21 patients (1.5%) had an absolute decrease of >10%, and ejection fraction was <50% compared with 16 patients (1.1%) in the placebo arm. There was an absolute decrease of ≥15% in 38 patients (2.7%) in the Nerlynx arm and in 48 patients (3.4%) in the placebo arm.

In the Nerlynx arm, of the 1,403 patients with baseline LVEF ≥50%, 3 (0.2%) had a post-baseline value of <40%, 30 (2.1%) had post-baseline values ≥40% but <50%, 1,150 (81.7%) patients did not change LVEF, and 220 (15.6%) were missing a post-baseline LVEF assessment. Among two patients (0.1%) with baseline LVEF <50%, one patient had a post-baseline value of ≥50%, and one patient had a missing post-baseline assessment. Three patients (0.2%) with missing baseline LVEFs had post-baseline values of ≥50%.

All Clinical Study Population

Cumulatively as of 01 May 2020, there were 657 AEs (11 serious) in 615 patients pertaining to the identified risk of cardiotoxicity in the clinical trials setting (n=6,605) resulting in an incidence rate of 9.3%.

A total of 191 AEs pertaining to cardiotoxicity occurred in 182 patients on neratinib monotherapy (n=2,777), resulting in an incidence rate of 6.6%. Of these 182 patients, 11 had grade 3 events and the remaining patients had grade 1 or grade 2 events; no grade 4 or grade 5 events were reported. Seven of the 182 patients had dose reductions; 32 led to permanent discontinuation of neratinib. The outcome of the events was reported as resolved in 95 patients, recovering in two patients, not recovered in 82 patients, unknown in five patients. Of the 182 patients, two patients had an SAE pertaining to cardiotoxicity, ejection fraction decreased, and oedema peripheral. Both patients were in the CONTROL trial. The first patient had an important medical event of stress-induced ejection fraction decreased secondary to a recent motor vehicular accident (2014US003554). The second patient with metastatic ovarian cancer status post bilateral salpingo-oophorectomy, infracolic omentectomy, rectosigmoid resection with anastomosis, and history of hydronephrosis with left ureteral obstruction, and deep venous thrombosis was hospitalised twice for oedema peripheral that was considered likely due to an underlying condition (2019US0048383).

A total of 226 events pertaining to cardiotoxicity occurred in 207 patients on neratinib combination therapy (n=1,301), resulting in an incidence rate of 16.0%; 54 (4.2%) in patients on N+C, 7 (0.5%) in (N+F), 6 (0.5%) in N+F+T, 93 (7.1%) in N+P, 14 (1.1%) in N+T, 39 (3.0%) in N+TS, and 13 (1.0%) in N+V. Of these 207 patients, 11 had grade 3 events, and the remaining patients had grade 1 or grade 2 events; no grade 4 or grade 5 events were reported. The outcome of the events was reported as recovered in 116 (8.9%) patients, recovering in 5 (0.4%) patients, not recovered in 69 (5.3%) patients, and unknown at the time of last follow-up in 2 (0.15%) patients. There were

six patients who had SAEs pertaining to cardiotoxicity, four in the N+P group, and one each in the N+C and N+F+T groups. Two of the patients in the N+P group had oedema peripheral (2008HK000594, 2012IL001283), one patient had ejection fraction decreased (2009IN000633) and one other patient had cardiac failure congestive (2011HU001989). Three of the four patients recovered and one patient with oedema peripheral had an outcome of persisted at the time of the last follow-up.

A total of 123 AEs pertaining to cardiotoxicity occurred in 119 patients on placebo (n=1,424), resulting in an incidence rate of 8.3%. One patient had an SAE of ejection fraction decreased that had an outcome of recovered (2012IT001643).

A cumulative review of these events did not identify a new safety finding or change the characteristic of this risk.

Post-authorisation

Cumulatively as of 01 May 2020, a total of 72 AEs (8 serious) in 70 patients have been received in the post-authorisation setting, resulting in a reporting rate of 0.016 per patient-year. Preferred Terms retrieved by the SMQs included peripheral swelling (n=47 [2 serious]), oedema peripheral (n=9), oedema (n=5), pulmonary oedema (n=4 [all serious]), ejection fraction decreased (n=3), cardiac failure congestive (n=2 [both serious]), cardiomegaly (n=1), and ventricular dysfunction (n=1).

No fatal AEs have been reported for this risk; none of the AEs had a severity reported. Ejection fraction decreased (n=3) was reported in a heavily-treated MBC patient who also had type 1 diabetes mellitus and polycystic ovarian syndrome (2020GB001951), and in two other patients where the AE was reported with insufficient details to allow for a meaningful causality assessment (2018US011000; 2018US011188). Cardiac failure congestive (n=2) was reported and attributed to prior treatment with HERCEPTIN® (trastuzumab), which is associated with congestive heart failure per its USPI (2017US014114), and also in a patient with history of the condition who was also on an unspecified organ transplant list (2018US010610). Cardiomegaly (n=1) and other AEs of mild mitral valve regurgitation and atrial enlargement diagnosed via an ECHO were reported in a patient with a history of lymphedema (2018US012938). Ventricular dysfunction (n=1) was reported with insufficient information to allow for a meaningful causality assessment (2019US001743).

Of the 72 reported AEs, outcome was not reported or unknown for most of the AEs (43 [59.7%]), 23 AEs (31.9%) were not resolved, and six AEs (8.3%) were resolving.

For case-level action taken with Nerlynx, the dose was not changed/not applicable for 18 cases (25%), temporarily withheld for 18 cases (25%), discontinued for 18 cases (25%), decreased/reduced for 12 cases (16.7%), increased for 3 cases (4.2%), and unknown for 3 cases (4.2%).

A cumulative review of these PTs retrieved by the SMQs for this risk did not identify any new safety findings or change the characteristic of this risk.

Background incidence/prevalence:

Congestive heart failure, NYHA II – IV or asymptomatic cardiac dysfunction, including reduced ventricular ejection fraction, is a common adverse reaction associated with the use of trastuzumab. The cumulative incidence of heart failure or cardiomyopathy in BC patients reported within three years after diagnosis was 18.1% for non-treated patients and 32.1% in patients who received adjuvant trastuzumab therapy (versus 17.2% in cancer-free control patients, Chen et al, 2012).

Risk groups or risk factors:

Cardiovascular side effects of TKIs are varied and have included heart failure, left ventricular dysfunction, conduction abnormalities, QT prolongation, acute coronary syndromes, myocardial injury, arterial thromboses, and hypertension. Overall, systolic dysfunction with resultant heart failure is one of the most common important side effects of TKI treatment (Chen et al, 2008).

According to the American College of Cardiology and the American Heart Association, patients at high risk for developing heart failure are those with hypertension, coronary artery disease, diabetes mellitus, family history of cardiomyopathy, use of cardiotoxins, and obesity, who have no structural heart disease at present. Patients with asymptomatic heart failure but with structural heart disease (previous myocardial infarction, left ventricular remodelling including left ventricular hypertrophy and low ejection fraction, or asymptomatic valvular disease) are at risk of further left ventricular remodelling leading to development of heart failure symptoms.

Treatment with anthracycline chemotherapy has been associated with a cumulative dose-dependent decrease in LVEF, which were asymptomatic for the most part. This progressive cardiotoxicity usually occurs after the completion of treatment with anthracyclines and may become apparent within one year of the completion of treatment (early onset chronic cardiotoxicity) or many years after chemotherapy has been completed (late onset chronic cardiotoxicity). Other risk factors have been identified that increase the risk of anthracycline-induced cardiotoxicity, such as concomitant treatment with cyclophosphamide, trastuzumab, or paclitaxel. The interaction between anthracyclines, such as doxorubicin, and trastuzumab, is of particular interest, given the relatively common use of the latter agent for adjuvant therapy for BC (Volkova and Russell, 2011).

Potential mechanisms:

Cardiotoxicity of a targeted agent was first reported for trastuzumab, the monoclonal antibody that targets the HER2 receptor. Because HER2 appears to play an important role in the proliferation and survival of cardiomyocytes, systemic administration of trastuzumab results in on-target toxicity by interfering with the HER2 functioning in cardiac tissue, which manifests as left ventricular systolic dysfunction. However, other observations argue that the story could be more complex. If inhibition of HER2 signalling induces cardiomyocyte dysfunction, then cardiotoxicity would also be expected with small-molecule inhibitors of HER2 kinase activity (Force et al, 2007). However, clinical results with HER2 TKI show variable cardiotoxicity (Lenihan and Kowey, 2013). To understand the basic mechanism of cardiomyopathy of TKIs, it is critical to understand 2 classes of toxicity. The first is "on-target" toxicity, wherein the tyrosine kinase target regulating cancer cell survival and/or proliferation also serve an important role in normal cardiomyocyte survival, and thus inhibition leads to myocardial dysfunction. "Off target" toxicity occurs when a TKI leads to toxicity via inhibition of a kinase not intended to be a target of the drug. This type of toxicity is intrinsically related to (a) the inherent nonselectivity of TKIs and (b) a trend toward "multi-targeting" designing drugs to inhibit a broad range of targets that includes kinases regulating both tumorigenesis and tumour angiogenesis (Chen et al, 2008). Although it has been possible to implicate critical kinases, inhibition of which leads to cardiotoxicity, it remains unclear whether left ventricular dysfunction with TKIs is attributable to myocyte loss (and therefore largely irreversible) or myocyte dysfunction (potentially reversible) (Cheng and Force, 2010).

One possibility is that immune-mediated effects on cardiomyocytes are responsible for trastuzumab cardiotoxicity. However, pertuzumab, another immunoglobin G1 monoclonal antibody that blocks HER2 dimerisation, is associated with a low frequency of cardiac dysfunction in early clinical trials. An alternative and intriguing explanation is that trastuzumab might trigger a unique intracellular signalling response in cardiomyocytes on binding to HER2. In BC cells, trastuzumab inhibits autophosphorylation of HER2/HER3 heterodimers. However, in rat cardiomyocytes, binding of a different anti-HER2 antibody not only reduced HER2 activation, but also triggered down-regulation of B-cell lymphoma (BCL)-extra-large and increased expression of short isoform, leading to loss of

mitochondrial membrane potential, a reduction in the level of ATP, cytochrome c release, and caspase activation. Unlike most tissues, neurons and cardiomyocytes are relatively resistant to apoptosis induced by cytochrome c release and caspase activation, possibly owing to increased expression of X-linked inhibitor of apoptosis and decreased expression of apoptotic protease activating factor 1. Consequently, antibody-mediated inhibition of HER2 might regulate mitochondrial integrity through the BCL-X proteins, leading to ATP depletion and contractile dysfunction without profound changes in cardiomyocyte ultrastructure. An HER2 kinase inhibitor might alter or abolish the effect of trastuzumab on BCL-X family proteins in cardiomyocytes, raising the interesting possibility that HER2 TKI might ameliorate trastuzumab cardiotoxicity. This would provide additional motivation for a trial that combines these two classes of agents (Force et al, 2007).

Preventability:

SmPC Section 4.4 describes that in patients with known cardiac risk factors, cardiac monitoring should be conducted, including assessment of LVEF, as clinically indicated. Monitoring may help to identify patients who develop cardiac dysfunction. Formal cardiac assessment prior to treatment should be considered in patients in whom there are cardiovascular concerns, especially in patients previously treated with anthracyclines or trastuzumab. In addition, caution should be exercised in treating patients with increased cardiac risk, e.g., hypertension, documented coronary artery disease, congestive heart failure, or LVEF of <55%.

Routine risk minimisation measures for cardiotoxicity are described in Part V.1., and additional risk minimisation measures are described in Part V.2.

Impact on individual patient:

Patients with reduced LVEF are at high risk for developing heart failure, which has a negative impact on the length and QoL of patients. Clinical manifestations of heart failure are often severe, culminating in acute or life-threatening conditions (Hoekstra et al, 2011).

Potential public health impact of safety concern

Considering this risk was observed more frequently in placebo-treated patients than Nerlynx-treated patients in controlled clinical studies, the impact on public health is expected to be low.

Evidence source

Non-clinical, clinical, and post-authorisation experience with neratinib treatment.

SVII.3.1.2.2. Important potential risk– Pulmonary toxicity (interstitial lung disease)

Search method: SMQ level 1: *Interstitial lung disease* (narrow and broad search)

The incidence, relative risk, outcome, and severity of ILD are presented for monotherapy with neratinib in Table SVII.25.

Table SVII.24: Important potential risk (neratinib monotherapy) – Pulmonary toxicity (interstitial lung disease)

	Randomised, blinded monotherapy breast cancer (ExteNET trial)			All monotherapy breast cancer studies
	Neratinib (N=1,408)		Placebo (N=1,408)	Neratinib (N=1710)
Incidence[a] n (%)	4 (0.3)		4 (0.3)	6 (0.4)
Relative risk[b]		1.000		
(95% confidence interval)		(0.251, 3.991)		
Incidence of serious events	0 (0.0)		1 (0.1)	0 (0.0)
Outcome[c]				
Resulted in death	0 (0.0)		0 (0.0)	0 (0.0)
Recovered	1 (0.1)		1 (0.1)	2 (0.1)
Did not recover	3 (0.2)		3 (0.2)	4 (0.2)
Missing	0 (0.0)		0 (0.0)	0 (0.0)
Severity[d]				
Worst grade=1	2 (0.1)		4 (0.3)	4 (0.2)
Worst grade=2	2 (0.1)		0 (0.0)	2 (0.1)
Worst grade=3	0 (0.0)		0 (0.0)	0 (0.0)
Worst grade=4	0 (0.0)		0 (0.0)	0 (0.0)
Worst grade=5	0 (0.0)		0 (0.0)	0 (0.0)
Missing grade	0 (0.0)		0 (0.0)	0 (0.0)

[a] All patients with at least one adverse event.
[b] Active versus Placebo/comparator.
[c] A patient with multiple events is counted once using the outcome of the last event.
[d] Grade was based on CTCAE V3.0 or above.
All Monotherapy breast cancer includes studies: 3144A1-201-WW, 3144A2-3003-WW, 3144A2-3004-WW, and PUMA-NER-6201
Program: Y:\stat\neratinib\meta\nda_ebc\iss\csr\program\rmp\t-rmp-eoi-sum.sas
Output: t02-01-06-eoi-pulm-bc.rtf (Date Generated: 18FEB2016:10:24) Source: adae, adsl

Nature of the risk:

In theory, Nerlynx may induce ILD as this risk was identified for similar compounds (class effect).

Clinical Trial with Monotherapy (ExteNET Trial)

During the ExteNET trial, pulmonary toxicity was reported by four Nerlynx-treated patients (0.3%) (versus four placebo-treated patients [0.3%]) including two patients with ILD (versus one patient in the placebo arm), one patient with pneumonitis (versus one patient in placebo arm), and one patient with pulmonary fibrosis (versus two patients in the placebo arm). These events i.e., ILD, pneumonitis, and pulmonary fibrosis, were considered treatment-related in three patients in the Nerlynx arm (0.2%) and two patients in the placebo arm (0.1%). Among Nerlynx-treated patients, two patients (0.1%) had grade 1 events and two patients (0.1%) had grade 2 events while all four patients (0.3%) in the placebo arm had grade 1 events. There were no grade >2 events. One patient in the placebo arm had serious pneumonitis and there were no serious pulmonary toxicity events in the Nerlynx arm. In the Nerlynx arm, two patients (0.1%) with pulmonary toxicity discontinued treatment (versus one patient in the placebo arm).

All Clinical Study Population

Cumulatively as of 01 May 2020, there were 38 AEs (8 serious) pertaining to the identified risk of pulmonary toxicity in the clinical trials setting. The 38 AEs pertaining to pulmonary toxicity occurred in a total patient population of 6,605, resulting in an incidence rate of 0.6%.

A total of nine AEs pertaining to pulmonary toxicity occurred in nine patients on neratinib monotherapy (n=2,777), resulting in an incidence rate of 0.3%. The events included pneumonitis (n=4), lung infiltration (n=2), ILD (n=2), and pulmonary fibrosis (n=2). Of these nine patients, one patient each had a grade 5 event and a grade 3 event; the remaining patients had grade 1 or grade 2 events; no grade 4 events were reported. Four patients had events that led to permanent discontinuation of neratinib; none had events that led to dose reduction of neratinib. The outcome of the events was reported as recovered in two patients, not recovered in six patients, and fatal in one patient. Two patients had SAEs of pneumonitis, the outcome in one patient was reported as not recovered, and in the other was fatal. The fatal event was in a patient who was taking neratinib for pancreatic adenocarcinoma with metastases to the liver and both lungs in the SUMMIT trial (2016ES003067). The other SAE was in a patient with BC with known metastasis to the lungs who experienced pneumonitis that led to study-drug discontinuation (2006US000252).

A total of 17 events pertaining to pulmonary toxicity occurred in 16 patients on neratinib combination therapy (n=1,301), resulting in an incidence rate of 1.2%; 1 (0.077%) patient on N+C, 6 (0.46%) on N+P, and 9 (0.77%) on N+TS. Of these 16 patients, three had grade 3 events, and the remaining patients had grade 1 or 2 events; no grade 4 or grade 5 events were reported. The outcome of the events was reported as resolved in seven patients, not recovered in six patients, and unknown at the time of the report in one patient. Two patients had SAEs of pneumonitis. One patient developed pneumonitis in the context of disease progression in the lungs while on treatment with N+TS for an unspecified solid tumour in Study 2205 (2011091645). The other case was in a patient who developed pneumonitis secondary to an infection with coagulase negative *Staphylococcus* while on treatment with N+P for an unspecified solid tumour in Study 203 (2008IN000617).

A total of four AEs pertaining to pulmonary toxicity occurred in four patients on placebo (n=1,424), resulting in an incidence rate of 0.3%. One SAE of pneumonitis was reported in a patient who received placebo in the ExteNET trial.

A cumulative review of these events did not identify a new safety finding or change the characteristic of this risk.

Post-authorisation

Cumulatively as of 01 May 2020, a total of three serious adverse reactions in three patients with MBC have been received in the post-authorisation setting, resulting in a reporting rate of 0.001 per patient-year. The PTs retrieved by the SMQ included pneumonitis (n=2) and pulmonary fibrosis (n=1).

No fatal AE has been reported, and none of the three serious adverse reactions had severity reported. Pneumonitis (n=2) (2019US004479; 2020GB001573) and pulmonary fibrosis (n=1) (2017US017544) were reported in patients with MBC. One of these patients was on concomitant letrozole and had a history of pneumonitis caused by prior trastuzumab treatment (2019US004479), another had a history of lung metastases with lung scarring (2017US017544), and the last one was taking concomitant capecitabine (2020GB001573).

Outcome was not reported for two AEs (pneumonitis, pulmonary fibrosis) and was unknown for pneumonitis. Case-level actions taken with Nerlynx for the AEs were dose discontinued (pneumonitis, pulmonary fibrosis) and dose temporarily withdrawn (pneumonitis), respectively.

A cumulative review of these PTs retrieved by the SMQ did not identify any new safety findings or change the characteristic of this risk.

Background incidence/prevalence:

Interstitial lung disease is a rare disease. During the ExteNET study, ILD was reported by 1 placebo-treated adult patient (0.1%) with early-stage HER2-overexpressed/amplified BC who had received prior adjuvant trastuzumab-based therapy. None of the placebo-treated patients reported lung infections.

Risk groups or risk factors:

As in cases associated with conventional antineoplastic drugs, pre-existing pulmonary fibrosis has been regarded as a risk factor for the development of ILD in targeted therapy. Other risk factors include male sex, a history of smoking, poor functional status, concomitant radiation therapy, absence of chemotherapy history, and a reduction in serum albumins (Min et al, 2011).

Potential mechanisms:

Although the link between EGFR inhibitors and ILD is poorly understood, as are the molecular mechanisms of pulmonary changes (Liu et al, 2007), a decrease in pulmonary epithelial cell regeneration through the blockade of EGFR-dependent phosphorylation may play an important role in the development of lung-selective toxicity of EGFR-TKIs (Sakao, 2012).

The pathogenesis of TKI-induced pulmonary toxicity may be explained by dividing the mechanism into acute and chronic processes. According to the original hypothesis regarding the pathogenesis of pulmonary fibrosis, acute injury appears to progress to chronic inflammation, aided by T-lymphocytes and macrophages. Continued exposure to an antigen or the failure of the lungs' intrinsic anti-inflammatory mechanisms has been suggested as a cause of persistent inflammation. Chronic inflammation stimulates the ability of fibroblasts to migrate, proliferate, and produce the extracellular matrix, thus leading to parenchymal fibrosis. The blockage of EGFR-dependent epithelial proliferation by EGFR-TKIs augments pulmonary fibrosis. One of the key initiating factors for the development of ILD is likely to be the apoptosis of non-neoplastic type I and II pneumocytes. Mitochondrial-mediated apoptotic pathways, which are activated in the lung tissues of patients suffering from idiopathic interstitial pneumonia, may be involved in the pathophysiology of the disease. While EGFR signalling probably represents yet another potential mechanism that helps to coordinate the process of recovery from lung injury by stimulating epithelial repopulation and restoration of barrier integrity, it is possible that EGFR inhibition, such as is seen with gefitinib therapy, will at least partially impair the ability of pneumocytes to respond to lung injury (Min et al, 2011).

Preventability:

Treatment of EGFR-TKI-induced ILD is largely supportive, including supplemental oxygen, empirical antibiotics, and mechanical ventilation. Immediate discontinuation of the drug is recommended, and systemic corticosteroids are usually prescribed, although no controlled trials have been conducted to evaluate their benefits (Min et al, 2011).

Routine risk minimisation measures for pulmonary toxicity are described in Part V.1., and additional risk minimisation measures are described in Part V.2.

Impact on individual patient:

The clinical manifestations of TKI-induced ILD are nonspecific and include cough, fever, dyspnoea, and hypoxemia. The patterns and severity of clinical manifestations may differ, depending on the patient's underlying illness and the relevant drug factors. Additionally, the time to onset of pulmonary complications is somewhat unpredictable.

Although it was reported that in 75% of cases, the complications occur within three months of gefitinib use, the majority of these complications do arise within four weeks of the therapy. In

another detailed analysis of 408 cases of ILD among 50,005 patients receiving study drug, the median time to onset of ILD was 24 days in the Japan group and 42 days in the USA group. Its clinical manifestations appear to be severe, occasionally culminating in acute or life-threatening conditions (Min et al, 2011).

Potential public health impact of safety concern:

Uncommon reports of pulmonary toxicity were received in patients treated with Nerlynx during the ExteNET trial, all of which were grade 1 or 2 events.

Overall, the public health impact is considered to be low.

Evidence source:

Non-clinical, clinical, and post-authorisation experience with neratinib treatment.

SVII.3.1.2.3. Important potential risk – Reproductive and developmental toxicity

Search method: SMQ level 1: *Pregnancy and neonatal topics* (narrow and broad search)

Nature of the risk:

There is no clinical trial experience with Nerlynx in pregnant women. In non-clinical studies, animals have experienced embryofoetal toxicity, birth defects, and death.

All Clinical Study Population

Cumulatively as of 01 May 2020, there were 29 AEs (7 serious) pertaining to the risk of reproductive and developmental toxicities in the clinical trials setting. The 29 AEs pertaining to reproductive and developmental toxicities occurred in a total patient population of 6,605, resulting in an incidence rate of 0.4%. All of these events occurred in adult patients.

A total of 12 AEs pertaining to reproductive and developmental toxicities occurred in 11 patients on neratinib monotherapy (n=2,777), resulting in an incidence rate of 0.4%. All the events occurred in adult patients. The events included mastitis (n=7, 0.3%) and 1 (0.04%) patient each had retracted nipple, uterine cervix stenosis, hypertrophic cardiomyopathy, and trachea-oesophageal fistula. There were two patients who had SAEs. The first patient had two SAEs of mastitis while on neratinib for BC (2007BE000398 and 2008BE000584). The second patient on treatment with neratinib for squamous cell carcinoma of the oesophagus with metastases to the bone, lymph nodes, and lungs developed leptomeningeal disease, seizure, aspiration pneumonia, trachea-oesophageal fistula, and atrial fibrillation while hospitalised for fatigue, diarrhoea, and dehydration (2017US008846). Of these 11 patients, two patients had grade 3 events (1 patient had 2 grade 3 events) and 9 had grade 2 events; no grade 1, grade 4 or grade 5 events were reported. None of the patients had events that led to dose reduction or permanent discontinuation. The outcome of the events was reported as recovered in eight patients and not recovered in four patients.

A total of seven events pertaining to reproductive and developmental toxicities occurred in seven patients on neratinib combination therapy (n=1,301), resulting in an incidence rate of 0.5%. One (0.1%) patient each was on N+F and N+F+T, 4 (0.3%) patients on N+P, and 2 (0.2%) patients on N+TS. All of the events occurred in adult patients. The events included two each of failure to thrive and omphalitis, and one each of chloasma, epidermolysis, and aplasia. Of these seven patients, one patient had a grade 4 event, one patient had a grade 3 event, and the remaining patients had grade 1 or grade 2 events; no grade 5 events were reported. One event of failure to thrive led to permanent discontinuation of study treatment with N+F and none led to dose reductions. The outcome of the events was reported as recovered in five patients and not recovered in two patients. There were three SAEs of failure to thrive (n=2) and aplasia (n=1). Failure to thrive was reported in two patients on treatment for metastatic BC, one on N+F (2017US004062) and the

other on N+TS (2011US002210), both of which had rapid progression of underlying disease resulting in failure to thrive.

A total of six AEs pertaining to reproductive and developmental toxicities occurred in six patients on placebo (n=1,424), resulting in an incidence rate of 0.4%. The events occurred in five patients who had mastitis and one patient with nipple inflammation.

A cumulative review of these events did not identify a new safety finding or change the characteristic of this risk.

Post-authorisation

Cumulatively as of 01 May 2020, a total of 10 AEs (5 serious) in 10 patients have been received in the post-authorisation setting, resulting in a reporting rate of 0.002 per patient-year. Apart from one pregnancy report (PT: pregnancy) all other PTs retrieved by the SMQs occurred in non-pregnant and non-lactating adults and consisted of failure to thrive (n=4 [3 serious]), and one AE each of apparent life-threatening event (serious), gene mutation, hereditary non-polyposis colorectal cancer syndrome (serious), mastitis, and neurofibromatosis.

No fatal AE has been received for this risk; none of the reported AEs had severity reported. Of the outcomes for the 10 AEs, one was not resolved (10.0%) and one was not reported/unknown for nine AEs (90.0%). For case-level actions taken with Nerlynx, the drug was discontinued in four cases (40.0%), temporarily withheld in three cases (30.0%), and unchanged in three cases (30.0%).

A cumulative review of these PTs retrieved by the SMQs for this risk did not identify any new safety findings or change the characteristic of this risk.

Background incidence/prevalence:

Breast cancer is one of the most common malignant neoplasms during pregnancy. Approximately 1 in 5 BCs diagnosed in women aged 25 to 29 years is associated with pregnancy, diagnosed either during pregnancy or during the first postpartum year. Moreover, the reported occurrence of BC diagnosed during pregnancy ranges from 2.4 to 7.3 per 100,000 pregnancies in population-based investigations. For most BC patients, pregnancies are either terminated to undergo conventional treatment or continued alongside adjusted treatment regimens. A Danish study found that 81% of pregnancies affected with BC were terminated during the first trimester (Loibl et al, 2015). As such, data pertaining to the incidence of foetus teratogenicity in untreated BC patients are sparse and limited to case reports.

In addition, available case series analyses of women with BC receiving chemotherapy during pregnancy suggest that the incidence of congenital anomalies ranges between 3.8% and 5.3% (McGrath and Ring, 2011).

Risk groups and risk factors:

Risk groups are women of childbearing potential, including women who are planning to become pregnant and pregnant women. Ineffective contraception is an important risk factor.

Potential mechanisms:

Embryofoetal lethality and foetal morphologic anomalies were observed in non-clinical studies and are a known drug-class effect. Embryofoetal lethality and/or morphologic anomalies (e.g., cleft palate/lip, effects on skull, ribs, and vertebrae) have been reported with other kinase inhibitors. Small molecules like TKIs can cross the placenta throughout the pregnancy period. Multi-TKIs are of particular concern given their potential interference with other vital physiological functions that could be necessary in foetal development (Lambertini et al, 2015).

Preventability:

SmPC Section 4.6 describes that women should avoid becoming pregnant while taking Nerlynx and for up to one month after ending treatment and that Nerlynx is not recommended during lactation. If Nerlynx is used during pregnancy, or if the patient becomes pregnant while taking Nerlynx, the patient should be apprised of the potential hazard to the foetus. Women should use highly effective contraceptive measures during treatment with Nerlynx and for one month after the end of therapy; women using systemically acting hormonal contraceptives should add a barrier method. Men should use a barrier method of contraception during treatment and for three months after the end of therapy. A cross reference is mentioned in SmPC Section 4.4.

Routine risk minimisation measures for reproductive toxicity are described in Part V.1., and additional risk minimisation measures are described in Part V.2.

Impact on individual patient:

Nerlynx may cause harm to the unborn child if it is taken by women who are pregnant.

Potential public health impact of safety concern:

Considering the usage of Nerlynx in the general population is not wide (i.e., only in adult patients with early-stage HER2-overexpressed/amplified BC, representing 4 to 19/100,000 cases; Ferlay et al, 2013; Wolff et al, 2013), there is no significant off-label use, women are advised to avoid becoming pregnant while taking Nerlynx and for up to one month after ending treatment, and Nerlynx is not recommended during lactation or in men not using a barrier method of contraception. The impact on public health is expected to be low.

Evidence source:

Non-clinical experience.

SVII.3.2 Populations in need of further characterisation

Elderly

Risk-benefit impact: In the Nerlynx arm of the ExteNET trial, there was a higher frequency of treatment discontinuations due to adverse reactions in patients aged 65 years and older than in patients less than 65 years old (Table SIV.16).

The serious adverse reactions most frequently reported in patients aged 65 years and older in the Nerlynx arm of the ExteNET trial were vomiting (4 patients [2.3%]), diarrhoea (3 patients [1.7%]), dehydration (2 patients [1.2%]), and renal failure (2 patients [1.2%]).

Post-authorisation

Using the year of birth of ≥65years (where present), a search of the safety database was conducted to retrieve cases of Nerlynx use in elderly patients in the post-authorisation setting.

Cumulatively, a total of 5,644 AEs occurring in 1,062 elderly patients have been received in the post-authorisation setting, resulting in a reporting rate of 1.291 per patient-year.

Cumulatively, a total of 27 AEs (18 serious) associated with renal impairment in the elderly population was retrieved using the MedDRA SMQ Acute renal failure in the safety database for a reporting rate of 0.006 per patient-year.

There are no specific safety concerns for elderly patients at this time. The Applicant will continue to monitor safety in patients who are 65 years of age or older to ensure the benefit-risk balance remains positive in this group. Review of applicable safety information will be provided routinely in PSURs.

Paediatric population

Risk-benefit impact: Nerlynx is not indicated for use in the paediatric population.

Pregnant and breastfeeding women

Risk-benefit impact: Pregnancy and breastfeeding are not recommended.

There is no experience with Nerlynx in pregnant or lactating women. There were no effects on mating or the ability of animals to get pregnant, but embryofoetal lethality and foetal morphologic anomalies (e.g., domed head, dilation of brain ventricles, and misshapen anterior fontanelles and enlarged anterior and/or posterior fontanelles) were observed.

No cases of exposure to neratinib during pregnancy were reported.

Women should avoid becoming pregnant while taking Nerlynx and for up to one month after ending treatment. Women of childbearing potential must use highly effective contraceptive measures during treatment and for one month after the end of therapy; women using systemically acting hormonal contraceptives should add a barrier method.

It is not known whether neratinib is excreted in human milk. A risk to newborns/infants cannot be excluded. No cases of exposure to neratinib during lactation were reported.

Patients with hepatic impairment

Risk-benefit impact: There are limited or no data on the clinical safety and efficacy of Nerlynx when administered to patients with significantly impaired hepatic function.

Section 4.2 of the SmPC indicates that no dose adjustment is required in patients with Child Pugh A or B (mild to moderate) hepatic impairment. Severe hepatic impairment (Child Pugh C) is contraindicated.

Patients with renal impairment

Risk-benefit impact: The population PK covariant analysis of mild to moderate renal insufficiency showed no clinically relevant effect on efficacy or safety endpoints. There is no experience with Nerlynx in patients with severe renal impairment. However, renal impairment is unlikely to affect the PK of Nerlynx given that the percentage of neratinib excreted in the urine is less than 0.5%. There is no experience with Nerlynx in patients with severe renal impairment since formal studies of patients with severe renal impairment have not been performed.

In the ExteNET trial, patients with mild or moderate renal impairment (CrCl 30 to 80 mL/min) compared with normal renal function (CrCl >80 mL/min) TEAEs and serious TEAEs were reported at the same frequency. Discontinuations were higher in the mild renal impairment patients (37.0% vs 6.6%) or moderate renal impairment (41.2% vs 5.6%) compared with patients with normal renal function (24.5% vs 5.2%, neratinib vs placebo, respectively) due to diarrhoea and dehydration.

Patients with cardiovascular impairment

Risk-benefit impact: Patients with clinically significant or uncontrolled cardiac disease, including congestive heart failure (NYHA functional classification of ≥2), angina requiring treatment myocardial infarction within the past 12 months, or any clinically significant supraventricular arrhythmia or ventricular arrhythmia requiring treatment or intervention were excluded from clinical studies.

Non-clinical and clinical studies did not indicate that there is a risk of cardiotoxicity. However, there is no experience with Nerlynx in patients with significant or uncontrolled cardiac disease.

Immunocompromised patients

Risk-benefit impact: There is no experience in immunocompromised patients treated with Nerlynx.

Patients with a disease severity different from inclusion criteria in clinical trials

Risk-benefit impact: Patients with brain metastases are routinely excluded from clinical trials testing new anticancer agents, due to poor ECOG status, prognosis, life expectancy, or lack of intact blood-brain barrier.

Patients with secondary malignancies were excluded from clinical studies to reduce confounding effects.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.25: Summary of safety concerns

Important identified risks	
Important identified risks	Gastrointestinal toxicity (diarrhoea and stomatitis[a]) Hepatotoxicity
Important potential risks	
Important potential risks	Cardiotoxicity (LVEF decreased) Pulmonary toxicity (ILD) Reproductive and developmental toxicity

Abbreviations: ILD = interstitial lung disease; LVEF = left ventricular ejection fraction.
[a]Includes mucosal inflammation, stomatitis, aphthous stomatitis, mouth ulceration, and oral mucosal blistering.

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

All the routine pharmacovigilance activities for Nerlynx are performed by Pierre Fabre Médicament following processes and procedures that are summarised in the current version of the Pharmacovigilance System Master File.

This routine pharmacovigilance includes the following:

- Systems and processes that ensure that information about all pharmacovigilance cases including suspected adverse reactions that are reported to the personnel of the company are collected.
- The preparation of reports for regulatory authorities:
- Expedited adverse drug reaction (ADR) reports.
- PSURs.
- Continuous monitoring of the safety profile including signal detection, issue evaluation, labelling update, and liaison with regulatory authorities.
- Other requirements, as defined by local regulations.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific adverse reaction follow-up questionnaire for hepatotoxicity:**

  A follow-up questionnaire is provided in case of hepatotoxicity to collect detailed information on patients' demographics, diagnostics, medical history, and risk factors.

  This form is provided in Annex 4 of this document.

- **Other forms of routine pharmacovigilance activities:**

  Not applicable.

III.2 Additional pharmacovigilance activities

Safety concerns and efficacy of risk minimisation measures will be assessed by routine pharmacovigilance activities. Furthermore, three post-authorisation safety studies (two interventional and one non-interventional studies) are considered as additional pharmacovigilance activities (Category 3) for diarrhoea.

Interventional clinical trial PUMA-NER-6201 summary

Study short name and title:

PUMA-NER-6201 - An open-label study to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and loperamide.

Rationale and study objectives:

The rationale of this study is to collect safety data in patients with early-stage HER2+ BC who have completed a prior course of adjuvant trastuzumab in order to expand the safety profile of neratinib when given concomitantly with intensive antidiarrheal prophylaxis for two cycles.

The primary objective of this study is to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib when administered with intensive loperamide prophylaxis, after prior treatment with trastuzumab.

Study design:

Observational, non-randomised, open-label.

Study population:

Patients with early-stage HER2+ BC.

Milestones:

Interim report 2: Q4 2020

Final Analysis: Planned Q4 2021

Post-authorisation safety study PUMA-NER-6202 summary-Protocol evaluation ongoing*

The evaluation of the 6202 protocol is on-going. Information presented here below is related to the last protocol version submitted by the MAH in June 2020.

PUMA-NER-6202 –A randomized Phase 2 study to evaluate the incidence of discontinuations due to diarrhoea at three months in patients with early-stage HER2-positive, hormone-receptor-positive BC treated with neratinib plus loperamide prophylaxis versus neratinib with initial dose escalation plus as-needed loperamide.

Study short name and title:

PUMA-NER-6202 – A randomized study to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and intensive loperamide prophylaxis versus neratinib with initial dose escalation plus as-needed loperamide.

Rationale and study objectives:

The study is planned to evaluate intensive loperamide prophylaxis versus neratinib with initial dose escalation plus as-needed loperamide in the first month of treatment in patients with early-stage HER2+ BC treated with Nerlynx.

The objective of the study is to characterise the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with the study drugs.

Study design:

Randomised.

Study population:

Patients with early-stage HER2+ BC treated with Nerlynx.

Milestones*:

Final Protocol: Q3 2020

Final Study Report: Planned Q2 2024

No interim analysis proposed

**will be revised with outcome of protocol assessment*

Observational study NER-7402 (Nerlyfe) summary

Study short name and title:

NER-7402 - Safety of neratinib among BC patients. A study to describe the incidence of discontinuation due to diarrhoea within the first three months of treatment with neratinib, in adult BC patients treated in extended adjuvant in a real-world setting, and the effectiveness of Nerlynx educational materials.

Rationale and study objectives:

This study is planned to describe the incidence of discontinuation due to diarrhoea within the first three months of treatment with neratinib, in adult BC patients treated in extended adjuvant in a real-world setting, and the effectiveness of Nerlynx educational materials.

Study design:

Observational.

Study population:

New users of Nerlynx.

Milestones:

Final Protocol: Q2 2020
Interim Report 1: Primary endpoint analysis from approximately the first 350 enrolled patients (for a 5% precision on the primary endpoint).
Interim Report 2: Primary endpoint analysis from all enrolled patients
Final Report: Estimated Q4 2024

III.3 Summary table of additional pharmacovigilance activities

Table III.3.26 : Ongoing and planned additional pharmacovigilance activities

Study and status	Summary of objectives	Safety concerns addressed	Milestones	Due date
Category 3 – Requires additional pharmacovigilance activities				
PUMA-NER-6201 An open-label study to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and loperamide Ongoing	To collect safety data in patients with early-stage HER2+ BC who have completed a prior course of adjuvant trastuzumab in order to expand the safety profile of neratinib when given concomitantly with intensive antidiarrheal prophylaxis for 2 cycles	Gastrointestinal toxicity (diarrhoea)		Interim 2: Q4 2020 Final: Q4 2021
PUMA-NER-6202 A randomized study to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and intensive loperamide prophylaxis versus neratinib with initial dose escalation plus as-needed loperamide. Planned-Protocol evaluation ongoing	To evaluate intensive loperamide prophylaxis versus initial dose escalation plus as-needed loperamide in the first month of treatment in patients with early-stage HER2+ BC treated with Nerlynx	Gastrointestinal toxicity (diarrhoea)	Final Protocol: Q3 2020* *Evaluation of the protocol including Milestones Ongoing).	Final: Q2 2024* *Evaluation of the protocol including Milestones Ongoing).
NER-7402 (Nerlyfe) Safety of neratinib among BC patients A study to describe the incidence of discontinuation due to diarrhoea within the first 3 months of treatment with neratinib, in adult breast cancer patients treated in extended adjuvant in a real-world setting, and the effectiveness of Nerlynx educational materials Planned-Protocol approved by PRAC	To describe the incidence of discontinuation due to diarrhoea within the first 3 months of treatment with neratinib, in adult BC patients treated in extended adjuvant in a real-world setting, and to evaluate the availability, interpretability, and the effectiveness of Nerlynx educational materials	Gastrointestinal toxicity (diarrhoea) Hepatotoxicity, cardiotoxicity (LVEF decreased), pulmonary toxicity (ILD), reproductive and developmental toxicity	Final Protocol: Q2 2020	Interim Report 1: Primary endpoint analysis from approximately the first 350 enrolled patients (for a 5% precision on the primary endpoint) Interim Report 2: Primary endpoint analysis from all enrolled patients Final: Q4 2024

Abbreviations: HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; PRAC = Pharmacovigilance Risk Assessment Committee.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine risk minimisation measures

Table V.1.27: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Gastrointestinal toxicity – Diarrhoea	Routine risk communication: SmPC Section 4.4 SmPC Section 4.8 Package Leaflet (PL) sections 2, 3 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Dose modifications and diarrhoea prophylaxis are included in SmPC Section 4.2 Instructions for diarrhoea management are included in SmPC Section 4.4 Instructions for patients for prophylactic treatment of diarrhoea are given in PL sections 2 and 3 Other risk minimisation measures beyond the Product information: Pack size: No specific adaptation Medicine's legal status: Prescription-only medicine. Use restricted to physicians experienced in the treatment of cancer.
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine risk minimisation measures: Monitor and evaluate post-authorisation and clinical trial safety data. Additional risk minimisation measure(s): None
Criteria for judging the success of the proposed risk minimisation measures	Routine risk minimisation measures: Stable or decreasing reporting trend analysis of post-authorisation safety data. Additional risk minimisation measure(s): Signal detection to include trend analysis to compare relative reported frequencies (actual versus historic) at monthly intervals and in scheduled PSURs to the European agencies. This will allow the identification of relative changes in reporting frequency (e.g., any decrease caused by introducing/updating risk management measures [RMM], or an increase caused by a drop in RMM effectiveness).

Safety concern	Routine risk minimisation activities
	Alerting regulatory authorities to an increase in the reporting rate; these reporting rates will be included in the PSURs. If there is a sustained increase (i.e., after an adjustment for stimulated reporting) in the reporting rate or if the pattern of severity worsens, Puma will alert regulators as soon as possible. It is anticipated that the reporting rate could increase temporarily as a result of increased awareness brought by the implementation of an RMP, patient support programme, and media attention.
Planned dates for assessment	Monthly trending analysis as part of signalling process.
Results of effectiveness measurement	Stable reporting observed.
Impact of risk minimisation	Achieving aim of stable reporting in post-authorisation surveillance and effective risk minimisation.
Comment	The MAH will continue to monitor adverse reactions of diarrhoea.
Gastrointestinal toxicity – Stomatitis	Routine risk communication: SmPC Section 4.8 and PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC and PL: none Other risk minimisation measures beyond the Product information: Pack size: No specific adaptation Medicine's legal status: Prescription-only medicine. Use restricted to physician experienced in the treatment of cancer.
Hepatotoxicity	Routine risk communication: SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Dose modifications for managing hepatotoxicity are included in SmPC Section 4.2 Instructions for monitoring of LFTs are presented in SmPC Section 4.4 Tests and checks for liver problems are described in PL section 2 and 4 and how to detect signs and symptoms of liver problems are presented in PL section 4

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Pack size: No specific adaptation Medicine's legal status: Prescription-only medicine. Use restricted to physician experienced in the treatment of cancer.
Important potential risks	
Cardiotoxicity – Left ventricular ejection fraction decreased	Routine risk communication: SmPC Section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Instructions for cardiac monitoring in patients with cardiac risk factors are presented in SmPC Section 4.4 Other routine risk minimisation measures beyond the Product Information: Pack size: No specific adaptation Medicine's legal status: Prescription-only medicine. Use restricted to physician experienced in the treatment of cancer.
Pulmonary toxicity – Interstitial lung disease	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Pack size: No specific adaptation Medicine's legal status: Prescription-only medicine. Use restricted to physician experienced in the treatment of cancer.

Safety concern	Routine risk minimisation activities
Reproductive and developmental toxicity	Routine risk communication: SmPC Section 4.4 SmPC Section 4.6 SmPC Section 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Instructions regarding women of childbearing potential and contraception in females and males are presented in SmPC Section 4.6 and information regarding pregnancy and contraception for the patient (male and female) in PL section 2 Other routine risk minimisation measures beyond the Product Information: Pack size: No specific adaptation Medicine's legal status: Prescription-only medicine. Use restricted to physician experienced in the treatment of cancer.

Abbreviations: MAH = Marketing Authorisation Holder; SmPC = Summary of Product Characteristics

V.2. Additional risk minimisation measures

Healthcare professional and patient training materials

Objective:

To provide educational resources to patients and HCPs to identify and minimize diarrhoea events.

Rationale for the additional risk minimisation activity:

The Marketing Authorisation Holder (MAH) has developed an educational program to be offered to patients and their healthcare providers in order to increase awareness of the risks associated with neratinib therapy by providing educational materials. They are designed to help physician and patients to manage diarrhoea and therefore reduce treatment discontinuations.

Target audience and planned distribution path:

The target audience, the relative educational materials and the planned distribution path (initial and ongoing distribution) are reported in the table below.

Target audience	Educational Materials (EM)	Planned distribution path
Patients	Patient information pack: ▪ Patient information leaflet ▪ A patient/carer treatment guide ▪ "My Treatment Journal"	Paper*: ▪ Given by the prescriber Electronically*: ▪ Via email or EMs available on a website (MAH website and/or NCA website*) **Left to the discretion of the MS*

HCP (Prescribers and/or pharmacists) Depending on the EU Member State (MS), the target prescribers and/or pharmacists include all healthcare providers who are expected to prescribe/dispense Nerlynx	Physician educational material ▪ The Summary of Product Characteristics ▪ Guide for healthcare professionals ▪ Patient educational material	Paper*: ▪ Distributed by medical representatives or ▪ Send by mail. Electronically*: Same path as patient **Left to the discretion of the MS*

Abbreviations: EM = educational materials; EU = European Union; MAH = Marketing Authorisation Holder; NCA = National Competent Authority; MS = member state

Plans to evaluate the effectiveness of the interventions and criteria for success:

The availability, interpretability, and effectiveness of Nerlynx educational materials (EM) will be evaluated in trial NER-7402 (Nerlyfe), and post-authorisation and clinical trial safety data will be monitored and evaluated.

V.3 Summary of risk minimisation measures

Table V.3.28: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Gastrointestinal toxicity – Diarrhoea	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL sections 2, 3, and 4 Additional risk minimisation measures: Healthcare professionals and Patient/Carer educational materials (see Annex 6)	Additional pharmacovigilance activities: PUMA-NER-6201 PUMA-NER-6202 PUMA-NER-7402
Gastrointestinal toxicity – stomatitis	Routine risk minimisation measures: SmPC Section 4.8. Additional risk minimisation measures: None	None
Hepatotoxicity	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.8 PL sections 2 and 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE follow-up form for hepatotoxicity

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Important potential risks		
Cardiotoxicity – LVEF decreased	Routine risk minimisation measures: SmPC Section 4.4 Additional risk minimisation measures: None	None
Pulmonary toxicity – Interstitial lung disease	None	None
Reproductive and developmental toxicity	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.6 SmPC Section 5.3 PL section 2 Additional risk minimisation measures: None	None

Abbreviations: AE = adverse event; PL = package leaflet; SmPC = Summary of Product Characteristics.

Part VI: Summary of the risk management plan

Summary of risk management plan for Nerlynx (neratinib)

This is a summary of the risk management plan (RMP) for Nerlynx. The RMP details important risks of Nerlynx, how these risks can be minimised, and how more information will be obtained about Nerlynx's risks.

Nerlynx's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to HCPs and patients on how Nerlynx should be used.

This summary of the RMP for Nerlynx should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 Nerlynx's RMP.

I. The medicine and what it is used for

Nerlynx is authorised as a single agent is indicated for the extended adjuvant treatment of adult patients with early-stage HRc+ HER2-overexpressed/amplified BC who completed adjuvant trastuzumab-based therapy less than one year ago. It contains neratinib as the active substance and it is given orally.

Further information about the evaluation of Nerlynx's benefits can be found in Nerlynx's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/medicines/human/EPAR/nerlynx

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Nerlynx, together with measures to minimise such risks and the proposed studies for learning more about Nerlynx's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised 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 minimise its risks.

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

In the case of Nerlynx, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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

II.A List of important risks

Important risks of Nerlynx are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Nerlynx. 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.

Table VI.II.A.29: List of important risks

Important identified risks	• Gastrointestinal toxicity - Diarrhoea and stomatitis[a] • Hepatotoxicity
Important potential risks	• Cardiotoxicity - LVEF decreased • Pulmonary toxicity - Interstitial lung disease • Reproductive and developmental toxicity

Abbreviations: LVEF = left ventricular ejection fraction.
[a] Includes mucosal inflammation, stomatitis, aphthous stomatitis, mouth ulceration, and oral mucosal blistering.

II.B Summary of important risks

Table VI.II.B.30: Important risks

Important identified risk: Gastrointestinal toxicity - Diarrhoea	
Evidence for linking the risk to the medicine	Non-clinical, clinical, and post-authorisation experience with neratinib treatment.
Risk factors and risk groups	For diarrhoea in general, groups at risk include patients with significant chronic active inflammatory bowel disease or recent acute GI disorder with diarrhoea as a major symptom (e.g., Crohn's disease, ulcerative colitis, malabsorption, or grade ≥2 diarrhoea of any aetiology prior to treatment). Aggravating risk factors include concomitant medications and other predisposing conditions including advanced age. For diarrhoea during treatment with TKIs, a small number of emerging clinical investigations have found an association between drug steady-state concentrations and diarrhoea, suggesting that gene variants within metabolic pathways for TKIs could play a role in toxicity susceptibility (Bowen, 2013).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL sections 2, 3, and 4 Additional risk minimisation measures: Provide patients and HPCs with educational material as additional resources to minimise diarrhoea (Annex 6).

Table VI.II.B.30: Important risks

Additional pharmacovigilance activities	PUMA-NER-6201. An open-label study to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and loperamide. Study PUMA-NER-6202 is being planned to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and intensive loperamide prophylaxis versus initial dose escalation plus as-needed loperamide. An observational study, NER-7402 (Nerlyfe), is being planned to describe the incidence of discontinuation due to diarrhoea within the first 3 months of treatment with neratinib, in adult BC patients treated in extended adjuvant in a real-world setting, and to evaluate the availability, interpretability, and effectiveness of Nerlynx EMs. The study will also evaluate the use of antidiarrheal medication among new users of Nerlynx, assess the effectiveness of Nerlynx therapy on QoL, and further assess and characterize events of hepatotoxicity, cardiotoxicity (LVEF decreased), pulmonary toxicity (ILD), reproductive and developmental toxicity. See Part II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Gastrointestinal Toxicity - Stomatitis	
Evidence for linking the risk to the medicine	Non-clinical, clinical, and post-authorisation experience with neratinib treatment.
Risk factors and risk groups	Among patient-related risk factors, comorbidities such as malnutrition and poor oral health can contribute relevantly to the risk of oral mucositis (stomatitis) (Seiler et al, 2014).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8. PL section 4 Additional risk minimisation measures: None
Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Non-clinical, clinical, and post-authorisation experience with neratinib treatment.
Risk factors and risk groups	Risk factors for DILI include increasing age, human immunodeficiency virus /acquired immunodeficiency syndrome infection and antiretroviral drug use, chronic hepatitis B or C infection, obesity, and non-alcoholic fatty liver disease. Patients taking anti-infectives, psychotropics, lipid-lowering agents, herbal and dietary supplements, and nonsteroidal anti-inflammatory drugs are also at risk (Bell et al, 2009). Severe toxic effects can be increased when TKIs are taken with a CYP3A4 inhibitor (Spraggs et al, 2013; Shah et al, 2013).

Table VI.II.B.30: Important risks

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.3 SmPC Section 4.4. SmPC Section 4.8. PL Section 2 and 4 Additional risk minimisation measures: None

Important potential risk: Cardiotoxicity - LVEF decreased	
Evidence for linking the risk to the medicine	Non-clinical, clinical, and post-authorisation experience with neratinib treatment.
Risk factors and risk groups	Cardiovascular side effects of TKIs are varied and have included heart failure, left ventricular dysfunction, conduction abnormalities, QT prolongation, acute coronary syndromes, myocardial injury, arterial thromboses, and hypertension. Overall, systolic dysfunction with resultant heart failure is one of the most common important side effects of TKI treatment (Chen et al, 2008). According to the American College of Cardiology and the American Heart Association, patients at high risk for developing heart failure are those with hypertension, coronary artery disease, diabetes mellitus, family history of cardiomyopathy, use of cardiotoxins, and obesity, who have no structural heart disease at present. Patients with asymptomatic heart failure but with structural heart disease (previous myocardial infarction, left ventricular remodelling including left ventricular hypertrophy and low ejection fraction, or asymptomatic valvular disease) are at risk of further left ventricular remodelling leading to development of heart failure symptoms. Treatment with anthracycline chemotherapy has been associated with a cumulative dose-dependent decrease in LVEF, which were asymptomatic for the most part. This progressive cardiotoxicity usually occurs after the completion of treatment with anthracyclines and may become apparent within one year of the completion of treatment (early onset chronic cardiotoxicity) or many years after chemotherapy has been completed (late onset chronic cardiotoxicity). Other risk factors have been identified that increase the risk of anthracycline-induced cardiotoxicity, such as concomitant treatment with cyclophosphamide, trastuzumab, or paclitaxel. The interaction between anthracyclines, such as doxorubicin, and trastuzumab, is of particular interest, given the relatively common use of the latter agent for adjuvant therapy for BC (Volkova and Russell, 2011).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Additional risk minimisation measures: none

Important potential risk: Pulmonary toxicity- Interstitial lung disease	
Evidence for linking the risk to the medicine	Non-clinical, clinical, and post-authorisation experience with neratinib treatment.
Risk factors and risk groups	As in cases associated with conventional antineoplastic drugs, pre-existing pulmonary fibrosis has been regarded as a risk factor for the development of ILD in targeted therapy. Other risk factors include male sex, a history of smoking, poor functional status, concomitant radiation therapy, absence of chemotherapy history, and a reduction in serum albumins (Min et al, 2011).
Risk minimisation measures	Routine risk minimisation measures: none Additional risk minimisation measures: none
Important potential risk: Reproductive and developmental toxicity	
Evidence for linking the risk to the medicine	Non-clinical experience.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.6 SmPC Section 5.3 PL Section 2 Additional risk minimisation measures: None

Abbreviations: AE = adverse event; ALP = alkaline phosphatase ALT = alanine aminotransferase; AST = aspartate aminotransferase; (AT) = aminotransferase; BC = breast cancer; CT = computerised tomography; DILI = drug-induced liver injury; ECHO = echocardiogram; GI = gastrointestinal; HCO = health care provider; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; L+C = lapatinib plus capecitabine; LVEF =left ventricular ejection fraction; MUGA = multigated acquisition scan; N+C = neratinib plus capecitabine; N+D = neratinib plus digoxin; N+F = neratinib plus fulvestrant; N+F+T = neratinib plus fulvestrant plus trastuzumab; N+P = neratinib plus paclitaxel; N+T = neratinib plus trastuzumab; N+TS = neratinib plus temsirolimus; N+V = neratinib plus vinorelbine; PL =; QoL = quality of life; SAE = serious adverse event; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event; TKI = tyrosine kinase inhibitor; ULN = upper limit of normal.

II.C Post-authorisation development plan

II.C.1 Studies that are conditions of the marketing authorisation

There are no post-authorisation safety trial category 1 or 2 or efficacy studies planned.

II.C.2 Other studies in post-authorisation development plan

Study PUMA-NER-6201 is being conducted to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib when administered with intensive loperamide prophylaxis, after prior treatment with trastuzumab.

Study PUMA-NER-6202 is being planned to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and intensive loperamide prophylaxis versus initial dose escalation plus as-needed loperamide in the first month of treatment.

An observational trial (NER-7402) is being planned to describe the incidence of discontinuation due to diarrhoea within the first three months of treatment with neratinib, in adult BC patients treated in extended adjuvant in a real-world setting, and to evaluate the availability, interpretability, and effectiveness of Nerlynx EMs. The trial will also evaluate the use of antidiarrheal medication among new users of Nerlynx, to assess the effectiveness of Nerlynx therapy on QoL.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex II: Planned and ongoing studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
PUMA-NER-6202* A randomized study to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and intensive loperamide prophylaxis versus neratinib with initial dose escalation plus as-needed loperamide Category 3 Planned	To characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and intensive loperamide prophylaxis versus initial dose escalation plus as-needed loperamide	- gastrointestinal toxicity (diarrhoea)	Final Protocol: Q3 2020* Final Study Report: Planned Q2 2024 * will be revised with outcome of protocol assessment
NER-7402 (Nerlyfe) A study to describe the incidence of discontinuation due to diarrhoea within the first 3 months of treatment with neratinib, in adult breast cancer patients treated in extended adjuvant in a real-world setting, and the effectiveness of Nerlynx educational materials Category 3 Planned	To describe the incidence of discontinuation due to diarrhoea within the first 3 months of treatment with neratinib, in adult BC patients treated in extended adjuvant in a real-world setting, and to evaluate the availability, interpretability, and the effectiveness of Nerlynx educational materials	- gastrointestinal toxicity (diarrhoea)	Protocol NER-7402 (Nerlyfe) Final Protocol: Q2 2020 Interim Report 1: Primary endpoint analysis from approximately the first 350 enrolled patients (for a 5% precision on the primary endpoint). Interim Report 2: Primary endpoint analysis from all enrolled patients Final Report: Estimated Q4 2024
PUMA-NER-6201 (CONTROL) An open-label study to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and loperamide Category 3 Ongoing	To collect safety data in patients with early-stage HER2+ BC who have completed a prior course of adjuvant trastuzumab in order to expand the safety profile of neratinib when given concomitantly with intensive antidiarrheal prophylaxis for 2 cycles	- gastrointestinal toxicity (diarrhoea)	Protocol PUMA-NER-6201 (CONTROL) Interim results 1: Dec 2018 Interim results 2: Q4/2020 Final study report submission: Planned Q4 2021

Annex 3 - Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan

Table of contents

Proposed Studies

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable.

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.

Ongoing studies

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority

Approved protocols for PASS PUMA-NER-6201:

EMEA/H/C/004030/0000 MEA 001:

Protocol PUMA-NER-6201 (CONTROL)

Approved protocols for PASS 7402 (CHMP endorsement dated 28-May-2020):

EMEA/H/C/004030/0000 MEA 003:

Protocol NER-7402 (Nerlyfe)

Annex 4 - Specific adverse drug reaction follow-up forms

Pierre Fabre	**Code :** FORM_CVI_11832	**N° version :** 3.0 Page **:** 1/105
Département émetteur : CORPORATE VIGILANCES		

ADVERSE DRUG REACTION COLLECTION FORM - NERLYNX® - LIVER FUNCTIONS TEST

File number: |__|__|__|__| - |__|__|__|__|__| *(for Pierre Fabre use only - Do not make any entry in this space)*

Reporter information:

Name: .....

Address: .....

Tel: .....

❑ Healthcare Professional: ❑ Physician ❑ Pharmacist ❑ Other: _____

❑ Patient

❑ Other: .....

Patient Identification

Last name (First 3 letters): |__|__|__| First name (First letter): |__| Sex: ☐ Male ☐ Female

Date of birth: ___/___/___ or Age: _____ Height: _____ Weight: _____

Past Medical History

Previous liver disorders: ☐ No ☐ Yes, specify (with dates and lab values):

_____

History of hepatitis: ☐ No ☐ Yes; Start date ___/___/___ Cause: _____

History of cirrhosis: ☐ No ☐ Yes; Start date ___/___/___

History of gallstones: ☐ No ☐ Yes; Start date ___/___/___

History of blood transfusions: ☐ No ☐ Yes; Start date ___/___/___

Previous Drug-Induced liver Injury:

_____ ☐ From ___/___/___ to ___/___/___

_____ ☐ From ___/___/___ to ___/___/___

_____ ☐ From ___/___/___ to ___/___/___

Other medical history:

_____

Concomitant diseases / Relevant history of hepatic conditions

Acute recent hypotension: ☐ No ☐ Yes; Start date ___/___/___

Biliary tract disorders: ☐ No ☐ Yes; Start date ___/___/___

Right heart failure: ☐ No ☐ Yes; Start date ___/___/___

HIV infection: ☐ No ☐ Yes; Start date ___/___/___

Herpes virus simplex infection: ☐ No ☐ Yes; Start date ___/___/___

Recent bacterial infection: ☐ No ☐ Yes; Start date ___/___/___

Alcohol use: ☐ No ☐ Yes - Start date ___/___/___ ☐ Ongoing

Other:

_____

Pierre Fabre	**Code :** FORM_CVI_11832	**N° version :** 3.0 Page **:** 2/105

Département émetteur : CORPORATE VIGILANCES

ADVERSE DRUG REACTION COLLECTION FORM - NERLYNX® - LIVER FUNCTIONS TEST

NERLYNX® 40mg film-coated tablet (Suspected PIERRE FABRE Drug Involved):

Daily dose & frequency: _____mg/day _____
Specify the indication: _____
Start date of treatment: ___/___/___ Specify if treatment is ongoing ☐
End date of treatment: ___/___/___ If unknown, specify duration of regimen: _____

Previous dose modifications of NERLYNX®:
☐ No ☐ Yes – Reason: _____Dose adjustment:_____

Concomitant Treatments if any (including self-medication products)

Herbal and dietary supplements: ☐ No ☐ Yes, specify: _____

Trade Name	Indication	Dosage/ Form	Suspect (tick box)	Start date	End date
			☐		
			☐		
			☐		
			☐		
			☐		

Adverse reaction (s):	Onset date	End date	Ongoing (Yes/No)	Grade NCI CTCAE
	___/___/___	___/___/___		
	___/___/___	___/___/___		
	___/___/___	___/___/___		

Description of adverse reaction(s) with symptom(s) including signs of severity (such as jaundice, hepatic encephalopathy with flapping tremor…) and provide further details, e.g. clinical findings, non-clinical findings (laboratory, imaging):

_____
_____
_____
_____
_____
_____

Pierre Fabre	**Code :** FORM_CVI_11832	**N° version :** 3.0 Page **:** 3/105

Département émetteur : CORPORATE VIGILANCES

ADVERSE DRUG REACTION COLLECTION FORM - NERLYNX® - LIVER FUNCTIONS TEST

Results of exams, please specify:

Serology of HAV: ☐ Negative ☐ Positive, with presence of anti-HAV IgM:

_____

Serology of HBV: ☐ Negative ☐ Positive, with presence of anti-HBc IgM:

_____

Serology of HCV: ☐ Negative ☐ Positive, value of ARN:

_____

Serology of HDV: ☐ Negative ☐ Positive, with presence of anti-delta IgG and ARN delta:

_____

Serology of HEV: ☐ Negative ☐ Positive, with presence of anti-HEV IgM and IgG:

_____

Serology of CMV: ☐ Negative ☐ Positive, with presence of anti-CMV IgM:

_____

Serology of EBV: ☐ Negative ☐ Positive, with presence of anti-VCA IgM:

_____

Presence of antinuclear antibodies (mitochondrial): ☐ No ☐ Yes

Test(s)	**Before treatment**		**During treatment**	
	Dates	**Results and units**	**Dates**	**Results and units**
AST	___/___/___		___/___/___	
	___/___/___		___/___/___	
	___/___/___		___/___/___	
ALT	___/___/___		___/___/___	
	___/___/___		___/___/___	
	___/___/___		___/___/___	
ALP	___/___/___		___/___/___	
	___/___/___		___/___/___	
	___/___/___		___/___/___	
Total bilirubin	___/___/___		___/___/___	
	___/___/___		___/___/___	
	___/___/___		___/___/___	
Direct/indirect bilirubin	___/___/___		___/___/___	
	___/___/___		___/___/___	
	___/___/___		___/___/___	

Pierre Fabre	**Code :** FORM_CVI_11832	**N° version :** 3.0 Page **:** 4/105

Département émetteur : CORPORATE VIGILANCES

ADVERSE DRUG REACTION COLLECTION FORM - NERLYNX® - LIVER FUNCTIONS TEST

Test(s)	Before treatment		During treatment	
GGT	___/___/___		___/___/___	
INR/PT	___/___/___		___/___/___	
	___/___/___		___/___/___	
	___/___/___		___/___/___	
Platelet count	___/___/___		___/___/___	
Other labs	___/___/___		___/___/___	

Please use additional pages if needed or attach relevant findings (e.g. labs, imaging, pathology report…)

Liver ultrasound/CT-scan (date and results):

_____

Liver biopsy (date and results):

_____

Presence of liver metastases: ☐ No ☐ Yes

Action taken No Yes

Did the adverse event lead to
Corrective treatment? ☐ ☐ If yes, treatment: _____

Following adverse event, Nerlynx® dose was:

Decreased ☐ Increased ☐ No change ☐ Discontinued ☐

If it was discontinued, did the event abate? ☐ ☐
If it was discontinued, was the product reintroduced? ☐ ☐
If yes, date product reintroduced: ___/___/___
If yes, did the event reoccur? ☐ ☐
If yes, date of reoccurrence: ___/___/___

Seriousness criteria:

☐ Death
☐ Life threatening
☐ Hospitalization or prolongation of existing from _____ to_____
☐ Disability/invalidity
☐ Congenital anomaly
☐ Judged as an important medical event
☐ Other reason, please specify:

Outcome:

Recovered/resolved	☐	Date of recovery: ___/___/___
Recovering/resolving	☐	
Not recovered/not resolved	☐	
Recovered/resolved with sequelae	☐	Specify: _____
Fatal	☐	Date of death: ___/___/___
Unknown	☐	

Pierre Fabre	**Code :** FORM_CVI_11832	**N° version :** 3.0 Page : 5/105

Département émetteur : CORPORATE VIGILANCES

ADVERSE DRUG REACTION COLLECTION FORM - NERLYNX® - LIVER FUNCTIONS TEST

Reporter's explanation about the causal relationship between the adverse reaction(s) and NERLYNX®

_____

_____

Has this case been notified to Competent Authorities? NO ☐ YES ☐

Last name[1], first name, address, qualification and/or stamp

Date: _____/_____/_____ Signature:

[1]The data collected about you will be subject to data processing in accordance with the provisions of the General Data Protection Regulation (GDPR) of April 27, 2016. All information and personal data that you share with us via this form will be protected and will remain confidential in accordance with our company policy and the regulation in force. The information you provide will be used for drug safety monitoring and may be shared with health authorities, the processing of your personal data being necessary for compliance with a legal obligation to which Pierre Fabre is subject. Please note that this personal data will be deleted or anonymized 10 years after marketing authorization withdrawal of our products. You have a right of access, to rectification and to restriction of processing of your personal data. You can exercise these rights by contacting us at generic email box dpofr@pierre-fabre.com. The processing of your data responding to legal requirement, be aware that your rights of opposition, deletion and portability are not applicable. You have the right to lodge a complaint with the national supervisory authority in charge of protection of personal data.

Annex 5 - Protocols for proposed and ongoing studies in RMP Part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities

Approved key messages of the additional risk minimisation measures

Prior to launch of Nerlynx in each Member State, the MAH must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Nerlynx is marketed, all healthcare professionals who are expected to prescribe/dispense Nerlynx, as well as all patients/carers who are expected to use Nerlynx, have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- Guide for HPCs
- Patient educational material
- **Guide for healthcare professionals:**
    - Name of the product, active substance, and approved indication of the product
    - Relevant information on the safety concern "Gastrointestinal toxicity (diarrhoea)" (e.g., seriousness, severity, frequency, time to onset, duration, reversibility of the AE as applicable)
    - Details of the population at higher risk for the safety concern
    - Key message to convey in patients counselling on how to prevent and minimise GI toxicity through appropriate monitoring and management:
        - **prophylactic treatment with antidiarrheal medicinal product (e.g., loperamide)**
        - **dietary changes**
        - **dose modification (with guideline to adjust doses)/ discontinuation of treatment**
- The importance of handing over the educational material to the patients/carers at the end of counselling
- Remarks on the importance of reporting ADRs

The patient information pack:

- Patient information leaflet
- A patient/carer treatment guide
- "My Treatment Journal"

- **The Patient/carer guide:**
    - Name of the product, active substance, and approved indication of the product
    - Relevant information of GI toxicity (diarrhoea) (e.g., signs and symptoms to be detailed [seriousness, severity, frequency, time to onset, duration, risks, and consequences])
    - Key messages on how to prevent and minimise GI toxicity through appropriate monitoring (with reference to treatment journal) and management:
        - **prophylactic treatment with antidiarrheal medicinal product (e.g., loperamide)**
        - **dietary changes**
        - **when to alert HCP and the importance of it for further treatment adjustment**
- Remark on importance of reading the PIL
- Remarks on the importance of reporting ADRs

Annex 7 - Other supporting data (including referenced material)

References

American Cancer Society. Breast Cancer Facts & Figures 2019-2020 [website]. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf. Accessed 02 July 2020a.

American Cancer Society. Europe. In The Cancer Atlas [website]. https://canceratlas.cancer.org/the-burden/europe/. Accessed 02 July 2020b.

Arteaga, C. L. et al. Treatment of HER2-positive breast cancer: current status and future perspectives. Nat. Rev. Clin. Oncol. 9, 16–32 (2011).

Assi HA, Khoury KE, Dbouk H, et al. Epidemiology and prognosis of breast cancer in young women. *J Thorac Dis.* 2013;5(Suppl 1):S2-S8.

Barcenas CH, Hurvitz SA, Di Palma JA, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: diarrheal toxicity in the CONTROL trial. *Ann Onc*. 2020 (forthcoming).

Bell L and Chalasani N. Epidemiology of idiosyncratic drug-induced liver injury. *Semin Liver Dis.* 2009;29(4):337-347.

Benusiglio PR, Lesueur F, Luccarini C, et al. Common ERBB2 polymorphisms and risk of breast cancer in a white British population: a case–control study. *Breast Cancer Res.* 2005;7:R204-R209.

Benusiglio PR, Pharoah PD, Smith PL, et al. HapMap-based study of the 17q21 ERBB2 amplicon in susceptibility to breast cancer. *Brit J Cancer.* 2006;95(12):1689–1695.

Bowen JM. Mechanisms of TKI-induced diarrhea in cancer patients. *Curr Opin Support Palliat Care.* 2013;7(2):162-167.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.

Breyer JP, Sanders ME, Airey DC, et al. Heritable variation of ERBB2 and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2009;18(4):1252–1258.

Cabanillas ME, Hu MI, Durand JB, et al. Challenges associated with tyrosine kinase inhibitor therapy for metastatic thyroid cancer. *J Thyroid Res.* 2011;2011:985780.

Chen J, Long JB, Hurria A, et al. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Coll Cardiol.* 2012;60(24):2504-2512.

Chen MH, Kerkelä R, Force T. Mechanisms of cardiac dysfunction associated with tyrosine kinase inhibitor cancer therapeutics. *Circulation.* 2008;118(1):84-95.

Cheng H and Force T. Molecular mechanisms of cardiovascular toxicity of targeted cancer therapeutics. *Circ Res.* 2010;106(1):21-34.

Cherny NI. Evaluation and management of treatment-related diarrhea in patients with advanced cancer: a review. *J Pain Symptom Manage.* 2008;36(4):413-423.

Collins LC, Marotti JD, Gelber S, et al. Pathologic features and molecular phenotype by patient age in a large cohort of young women with breast cancer. *Breast Cancer Res Treat.* 2012;131(3):1061-1066.

Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-E386.

Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. *Nat Rev Cancer.* 2007;7(5):332-344.

Han W, Kang D, Lee JE, et al. A haplotype analysis of HER-2 gene polymorphisms: association with breast cancer risk, HER-2 protein expression in the tumor, and disease recurrence in Korea. *Clin Cancer Res.* 2005;11(13):4775-4782.

Hardy KD, Wahlin MD, Papageorgiou I, et al. Studies on the role of metabolic activation in tyrosine kinase inhibitor–dependent hepatotoxicity: induction of CYP3A4 enhances the cytotoxicity of lapatinib in HepaRG cells. *Drug Metab Dispos.* 2014;42(1):162–171.

Hoekstra T, Lesman-Leegte I, van Veldhuisen DJ, et al. Quality of life is impaired similarly in heart failure patients with preserved and reduced ejection fraction. *Eur J Heart Fail.* 2011;13(9):1013-1018.

Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status*. J Natl Cancer Inst.* 2014;106(5):dju055.

Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States. *JAMA*. 2015;313(2):165-173.

Jhaveri KD, Wanchoo R, Sakhiya V, Ross D, Fishbane S. Adverse renal effects of novel molecular oncologic targeted therapies: a narrative review. *Kidney Int* Rep. 2017;2(1):108–123.

Kwan ML, Kushi LH, Weltzien E, et al, Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. *Breast Cancer Res.* 2009;11(3):R31.

Lambertini M, Peccatori FA, Azim HA Jr. Targeted agents for cancer treatment during pregnancy. *Cancer Treat Rev.* 2015;41(4):301-309.

Lenihan DJ and Kowey PR. Overview and management of cardiac adverse events associated with tyrosine kinase inhibitors. *Oncologist.* 2013;18(8):900-908.

Liu V, White DA, Zakowski MF, et al. Pulmonary toxicity associated with erlotinib. *Chest.* 2007;132(3):1042-1044.

Loibl S, Schmidt A, Gentilini O, et al. Breast cancer diagnosed during pregnancy: adapting recent advances in breast cancer care for pregnant patients. *JAMA Oncol.* 2015;1(8):1145-1153.

McGrath SE and Ring A. Chemotherapy for breast cancer in pregnancy: evidence and guidance for oncologists. *Ther Adv Med Oncol.* 2011;3(2):73-83.

Min JH, Lee HY, Lim H, et al. Drug-induced interstitial lung disease in tyrosine kinase inhibitor therapy for non-small cell lung cancer: a review on current insight. *Cancer Chemother Pharmacol.* 2011;68:1099-1109.

Momenimovahed Z and Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. *Breast Cancer (Dove Med Press)*. 2019;11:151–164.

Sakao S. Molecular mechanisms of lung‐specific toxicity induced by epidermal growth factor receptor tyrosine kinase inhibitors (Review). *Oncol Lett.* 2012;4(5):865-867.

Seiler S, Kosse J, Loibl S, Jackisch C. Adverse event management of oral mucositis in patients with breast cancer. *Breast Care (Basel).* 2014;9(4):232-237.

Shah DR, Dholakia S, Shah RR. Effect of tyrosine kinase inhibitors on wound healing and tissue repair: implications for surgery in cancer patients. *Drug Saf.* 2014;37(3):135-149.

Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. *Drug Saf.* 2013;36(7):491-503.

Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987;235(4785):177-182.

Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science.* 1989;244(4905):707-712.

Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer.* 2004;100(9 Suppl):1995–2025.

Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA*. 2001;98(19):10869-10874.

Spraggs CF, Xu CF, Hunt CM. Genetic characterization to improve interpretation and clinical management of hepatotoxicity caused by tyrosine kinase inhibitors. *Pharmacogenomics.* 2013;14(5):541-554.

Van Sebille YZ, Gibson RJ, Wardill HR, et al. ERBB small molecule tyrosine kinase inhibitor (TKI) induced diarrhoea: chloride secretion as a mechanistic hypothesis. *Cancer Treat Rev.* 2015;41(7):646-652.

Verma R, Bowen RL, Slater SE, et al. Pathological and epidemiological factors associated with advanced stage at diagnosis of breast cancer. *Brit Med Bull.* 2012;103(1):129–145.

Volkova M, and Russell R. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. *Curr Cardiol Rev.* 2011;7(4):214-220.

Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol.* 2013;31(31):3997-4013.

World Health Organization. Breast cancer and prevention [website]. https://www.who.int/cancer/detection/breastcancer/en/. Accessed -2 July 2020.

Yedjou CG, Sims JN, Miele L, et al. Health and racial disparity in breast cancer. *Adv Exp Med Biol*. 2019;1152:31–49.

Annex 8 – Summary of changes to the risk management plan over time

Version	**Approval date** **Procedure**	**Change**
0.9	EMEA/H/C/004030/000003-JUL-2018	Initial RMP
1.1	EMEA/H/C/004030/II/0020	• Addition of a new important identified risk • Update concerning the post-authorisation safety studies
1.2	EMEA/H/C/004030/II/0020	• During the evaluation procedure, the inclusion of the risk of renal failure in the RMP as a safety concern was not accepted. This risk was removed from the relevant sections.
2.0	EMEA/H/C/004030/II/0020	• Approved and signed version by QPPV submitted for closing sequence