

## EU RISK MANAGEMENT PLAN FOR ROZLYTREK<sup>®</sup>/ENTRECTINIB

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### **Rationale for Submitting an Updated RMP**

A post authorization measure (PAM) has been submitted to the European Medicines Agency (EMA) for approval of Study BO41932 (TAPISTRY) as an additional trial to fulfil the Rozlytrek specific obligation (SOB). This EU RMP is updated to version 3.1 post approval of PAM.

### **Summary of Significant Changes in This RMP**

Inclusion of the TAPISTRY (BO41932) study as a post-approval efficacy study.

Update of annexes 3 and 5 with current protocol versions of ongoing studies.

### **Other RMP Versions under Evaluation**

RMP Version Number: Not applicable

Submitted on: Not applicable

Procedure Number: Not applicable

### **Details of Currently Approved RMP**

RMP Version Number: 2.0

Approved with Procedure Number: EMEA/H/C/004936/0000

Date of approval (opinion date): 29 May 2020

See [page 1](#) for signature and date

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Dr PPD (Deputy EU QPPV)

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Date

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Date

## PART I: PRODUCT OVERVIEW

**Table 1 Product Overview**

|   |   |
|---|---|
| Active Substance(s)<br>(INN or common name)   | Entrectinib   |
| Pharmacotherapeutic group(s) (ATC Code)       | L01XE14   |
| Marketing Authorization Holder (or Applicant) | Roche Registration GmbH   |
| Medicinal products to which this RMP refers   | One   |
| Invented name(s) in the EEA                   | Rozlytrek®  |
| Marketing authorization procedure             | Centralized   |
| Brief description of the product              | <p><b>Chemical class:</b> Antineoplastic agent, Tyrosine Kinase inhibitor</p> <p><b>Summary of mode of action:</b> Entrectinib is a central nervous system (CNS) active, potent inhibitor of the receptor tyrosine kinases tropomyosin receptor kinases A, B and C (TRKA, TRKB and TRKC; encoded by the genes NTRK1, NTRK2, and NTRK3, respectively), ROS proto-oncogene 1 receptor tyrosine kinase (encoded by the gene ROS1), and anaplastic lymphoma kinase (ALK; encoded by the gene ALK). Gene rearrangements (fusions) in each of the genes encoding these target kinases have the potential to be oncogenic drivers, tend to be mutually exclusive, and have been observed in a variety of tumour types.</p> <p><b>Important information about its composition:</b></p> <ul style="list-style-type: none"><li>• Each 100 mg hard capsule contains 65 mg lactose. Each 200 mg hard capsule contains 130 mg lactose.</li><li>• 200 mg hard capsules contain 0.6 mg of the azo colouring agent sunset yellow FCF (E 110, FD&amp;C yellow #6).</li></ul> |
| Hyperlink to the Product Information          | Refer to Product Information  |



|   |  |
|---|--|
| Indication(s) in the EEA  | <p>Current:</p> <p>Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,</p> <ul style="list-style-type: none"> <li>• who have a disease that is locally advanced, metastatic or where surgical resection is likely to</li> <li>• result in severe morbidity, and</li> <li>• who have not received a prior NTRK inhibitor</li> <li>• who have no satisfactory treatment options</li> </ul> <p>Rozlytrek as monotherapy is indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.</p> <p>Proposed: Not applicable.</p> |
| Dosage in the EEA   | <p>Current:</p> <p><b>Adults</b></p> <p>The recommended dose of entrectinib for adults is 600 mg given orally, once daily.</p> <p><b>Paediatric patients</b></p> <p>The recommended dose for paediatric patients 12 years of age and older, is 300 mg/m<sup>2</sup> body surface area (BSA) entrectinib once daily. The 100 mg (size 2) capsules are recommended for paediatric patients</p> <p>Proposed: Not applicable.</p>  |
| Pharmaceutical form(s) and strengths  | <p>Current:</p> <ul style="list-style-type: none"> <li>• Each 100 mg hard capsule contains 100 mg entrectinib</li> <li>• Each 200 mg hard capsule contains 200 mg entrectinib</li> </ul> <p>Proposed: Not applicable.</p>  |
| Is or will the product be subject to additional monitoring in the European Union? | Yes  |

ALK=anaplastic lymphoma kinase; BSA=body surface area; EEA=European Economic Area; NSCLC=Non-small cell lung cancer; NTRK=Neurotrophic Receptor Tyrosine Kinase; RMP=risk management plan; SmPC=Summary of Product Characteristics; TRK=tropomyosin receptor kinases.

## GLOSSARY OF ABBREVIATIONS

| Abbreviation | Definition                                     |
|--------------|--|
| ADR          | adverse drug reaction                          |
| AE           | adverse event                                  |
| ALK          | anaplastic lymphoma kinase receptor            |
| ALT          | alanine aminotransferase                       |
| AST          | aspartate aminotransferase                     |
| AUC          | area under the curve                           |
| BDNF         | brain-derived neurotrophic factor              |
| CCOD         | clinical cut-off date                          |
| CHF          | congestive heart failure                       |
| DDI          | drug-drug interaction                          |
| HLGT         | high level group term                          |
| HLT          | high level term                                |
| CHF          | Congestive heart failure                       |
| CHMP         | committee for medicinal products for human use |
| CI           | confidence interval                            |
| COPD         | chronic obstructive pulmonary disease          |
| CNS          | central nervous system                         |
| dmNTS        | dorsal medial nucleus tractus solitarius       |
| ECG          | Electrocardiogram                              |
| hERG         | human ether-a-go-go-related gene               |
| LoQ          | list of questions                              |
| LTP          | long-term potentiation                         |
| MAA          | marketing authorisation application            |
| MASC         | mammary analogue secretory carcinoma           |
| mDOR         | median duration of response                    |
| MI           | myocardial infarction                          |
| MTD          | maximum tolerated dose                         |
| NGF          | nerve growth factor                            |
| NGS          | next generation sequencing                     |
| NR           | not reached                                    |
| NSCLC        | non-small cell lung cancer                     |
| NTRK         | neurotrophic tyrosine receptor kinase          |
| ORR          | objective response rate                        |
| PK           | Pharmacokinetic                                |
| PT           | preferred term                                 |
| GIST         | gastrointestinal stromal tumors                |

|       |                                      |
|-------|--------------------------------------|
| EIAED | enzyme inducing antiepileptic drugs, |
| CYP   | Cytochrome P450                      |
| QTc   | corrected QT interval                |
| RMP   | Risk Management Plan                 |
| SmPC  | Summary of Product Characteristics   |
| SMQ   | Standardised MedDRA Query            |
| SRS   | stereotactic radiosurgery            |
| TKI   | tyrosine kinase inhibitor            |
| TRK   | tropomyosin receptor kinase          |
| WBRT  | whole-brain radiotherapy             |

## **PART II: SAFETY SPECIFICATION**

### **PART II: MODULE SI – EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)**

#### **S I.1 INDICATION(S)**

##### **SI.1.1 ADULT AND PAEDIATRIC PATIENTS 12 YEARS OF AGE AND OLDER WITH SOLID TUMOURS THAT HAVE A NTRK GENE FUSION (please refer to approved label for full wording)**

Neurotrophic Tyrosine Receptor Kinase (NTRK) fusions are rare events in common cancers (e.g., frequency of <1% in non-small cell lung cancer [NSCLC, see [SI.1.2](#) for details on NSCLC] and 1–2% in colorectal cancer [CRC]). Fusions are more frequently observed in some rare cancers (e.g., 90–100% of mammary secretory carcinomas [MASC], a rare form of salivary gland cancer, which in turn represents <1% of all cancer malignancies). NTRK fusions have also been observed in papillary thyroid cancer, melanoma, and sarcoma.

Considering the rarity of NTRK fusion-positive solid tumours and differences in testing methodologies, the exact frequency of NTRK fusions in solid tumours remains unclear. Prevalence data in the literature and published studies are based on small number of cases, and variations in frequencies among different studies and tumour subtypes may be biased by screened study cohorts and NTRK fusion detection techniques.

Based on next generation sequencing (NGS) profiling of 116,398 adult and paediatric tumour samples using the Foundation Medicine Inc (FMI) NGS platform, an estimated prevalence of 0.32% has been observed. Screening estimates from the entrectinib clinical trials indicate the prevalence to be as high as 1%, i.e., approximately 90 NTRK fusions detected in about 10,000 patient tumour samples tested at Ignyta's Clinical Laboratory Improvement Amendments lab, although this population may be enriched based on local pre-screening testing. Therefore, estimates of the frequency of NTRK fusions are in the range of 0.32%–1% across tumour types. This is comparable with estimates of the prevalence of NTRK fusions by genomic profiling reported in the literature using high-throughput NGS on tumours from a large and broad cohort of cancer patients (0.25% [MSK-IMPACT assay; [Zehir et al. 2017](#)]).

#### **Paediatric Patients**

Childhood cancer incidence has long been noted to vary by age, sex, and race/ethnicity. Overall, the incidence is highest in infancy at about 240 cases per million per year. This rate drops to approximately 128 cases per million at 5–9 years of age before rising to 220 cases per million at 15–19 years of age ([Howlader et al. 2016](#)). All the embryonal tumours (i.e., neuroblastoma, Wilm's tumour, retinoblastoma, etc.) share a downward sloping incidence which starts high at birth and dissipates after about 5 years of age. Acute lymphoblastic leukemia is notable for the incidence peak which occurs between 2–5 years of age, while bone sarcoma incidence peaks sharply around the time of the

pubertal growth spurt in early-to mid-adolescence. For most childhood cancers there is a slight male preponderance. The male-to-female ratio ranges from 1.04–1.64 in neuroblastoma and germ cell tumours, respectively, in cases 0–19 years of age but varies considerably by age group and more specific diagnosis. Childhood cancer risk also differs by race/ethnicity. Relative to White children in the U.S. the incidence of most types of cancer is lower in black, Asian, and Hispanic children ([Spector et al. 2015](#)).

As with adults, tumours with NTRK gene fusions are rare in paediatric/adolescent patients. Two recent publications on genomic profiling of paediatric cancers reported that the prevalence of NTRK fusions ranged from 0.44% (9/2031 samples from patients ≤20 years; [Pavlick et al. 2017](#)) to 0.49% (6/1215 samples from patients ≤18 years; [Chmielecki et al. 2017](#)).

- **Demographics**

The low prevalence of NTRK fusions in adult and paediatric patients across a number of tumour types means that demographic data are limited.

- **The main existing treatment options**

Considering the broad cancer types that may be sensitive to pan-TRK inhibition, [Table 2](#) summarizes the efficacy of currently approved or available treatment options for patients with select tumour types that have been reported to harbor NTRK fusions and who have either progressed following prior therapies or who have no acceptable standard therapies. Overall, the prognosis is poor, even in this broader patient population with objective response rate (ORRs) ranging from 0%–47. 2%.

**Table 2 Efficacy of Approved or Available Therapies for Patients with Tumour Types Reported to Harbor NTRK Fusions and Who Have Either Progressed Following Prior Therapies or Who Have No Acceptable Standard Therapies**

|   | Therapy                             | Line of treatment | ORR (%) | mDOR (month) | PFS (month) | mOS (month) | Reference                 |
|---|-------------------------------------|-------------------|---------|--------------|-------------|-------------|---------------------------|
| Non Small-cell Lung Cancer (EGFR or ALK negative) | Docetaxel                           | 2L                | 6.8     | 6.0          | 2.8 (TTP)   | 7.9         | Sheperd et al. 2000       |
|   | Pemetrexed                          | 2L                | 9.1     | 4.6          | 2.9         | 8.3         | Hanna et al 2004          |
|   | Bevacizumab+paclitaxel              | 2L or 3L          | 22.5    | NA           | 5.4         | 9.9         | Cortot et al. 2016        |
|   | Docetaxel+Ramucirumab               | 2L                | 22.9    | NA           | 4.5         | 10.5        | Garon et al. 2014         |
|   | Pembrolizumab <sup>a</sup>          | ≥2L               | 18.5    | NR           | 4.0         | 12.7        | Herbst et al. 2016        |
|   | Docetaxel+Nintedanib                | 2L                | 4.7     | NA           | 3.4         | 12.6        | Reck et al. 2014a         |
|   | Nivolumab                           | ≥2L               | 19.2    | 17.2         | 2.3         | 12.2        | Borghaei et al. 2015      |
| Colorectal Carcinoma                              | Cetuximab+irinotecan <sup>b</sup>   | 2L                | 16.4    | 5.7          | 4.0         | 10.7        | Sobrero et al. 2008       |
|   | Panitumumab+FOLFIRI <sup>b</sup>    | 2L                | 35.4    | 7.6          | 5.9         | 14.5        | Peeters et al. 2010       |
|   | Bevacizumab+FOLFOX-4                | 2L                | 22.7    | NA           | 7.3         | 12.9        | Giantonio et al. 2007     |
|   | Aflibercept+FOLFIRI                 | ≥2L               | 19.8    | NA           | 6.9         | 13.5        | Van Cutsem et al. 2012    |
|   | Ramucirumab+FOLFIRI                 | 2L                | 13.4    | NA           | 5.7         | 13.3        | Taberero et al. 2015      |
|   | Regorafenib                         | ≥2L               | 1.0     | NA           | 1.9         | 6.4         | Grothey et al. 2013       |
|   | Trifluridine/Tipiracil              | ≥2L               | 1.6     | NA           | 2.0         | 7.1         | Mayer et al. 2015         |
| Breast Cancer incl. secretory breast              | Gemcitabine+Paclitaxel              | ≥2                | 41.4    | 9.9          | 6.1 (TTP)   | 18.6        | Albain et al. 2008        |
|   | Lapatinib+Capecitabine <sup>c</sup> | ≥2                | 22      | 9.9          | 5.5 (TTP)   | 17.0        | Cameron et al. 2008; 2010 |
|   | Capecitabine+Docetaxel              | ≥2L               | 41.6    | 7.3          | 6.1 (TTP)   | 14.5        | O'Shaugnessy et al. 2002  |
|   | Fulvestrant+Palbociclib             | ≥2L               | 24.6    | 9.3          | 9.5         | NA          | Cristofanilli et al. 2016 |
|   | Eribulin                            | ≥2L               | 12.2    | 4.2          | 3.7         | 13.2        | Cortes et al. 2011        |
| Salivary Gland Cancer (incl. MASC)                | Sunitinib                           | ≥1L               | 0       | NA           | 7.2 (TTP)   | 18.7        | Chau et al. 2012          |
|   | Gefitinib                           | ≥1L               | 0.0     | NA           | 4.3/2.1     | 25.9/16.0   | Jakob et al. 2015         |
|   | Platinum+Gemcitabine                | ≥1L               | 24.2    | 6.7          | NA          | 13.8        | Laurie et al. 2010        |

|                     | Therapy                  | Line of treatment | ORR (%) | mDOR (month) | PFS (month) | mOS (month) | Reference                 |
|---------------------|--------------------------|-------------------|---------|--------------|-------------|-------------|---------------------------|
| Soft Tissue Sarcoma | Eribulin <sup>d</sup>    | ≥2L               | 4.0     | NA           | 2.6         | 13.5        | Schöffski et al. 2016     |
|                     | Sunitinib <sup>e</sup>   | 2L                | 6.8     | NA           | 24.1        | 72.7        | Demitri et al. 2006       |
|                     | Regorafenib <sup>e</sup> | ≥2L               | 4.5     | NA           | 1.1-5.6     | 4.7-21.0    | Mir et al. 2016           |
|                     | Trabectedin              | ≥2L               | 9.9     | 6.5          | 4.2         | 12.4        | Demetri et al 2016        |
|                     | Pazopanib <sup>f</sup>   | ≥2                | 4.0     | 9.7          | 4.6         | 12.6        | van der Graaf et al. 2012 |
|                     | Dacarbazine+ Gemcitabine | ≥2L               | 12      | 10.2         | 4.2         | 16.8        | García et al. 2011        |
|                     | Olaratumab+ Doxorubicin  | ≥1L <sup>g</sup>  | 18.2    | 8.3          | 6.6         | 26.5        | Tap et al. 2016           |

MASC= mammary secretory carcinomas; mDOR= median duration of response; mOS= median overall survival; NA= not available; NR= not reached; ORR=objective response rate; PFS=progression free survival; TTP= time to progression.

<sup>a</sup> In patients with PD-L1 expression on at least 1% of tumour cells.

<sup>b</sup> For patients with RAS wild type tumours.

<sup>c</sup> Patients with HER2-positive advanced/metastatic breast cancer.

<sup>d</sup> For patients with liposarcomas.

<sup>e</sup> Patients with unresectable and/or metastatic gastrointestinal stromal tumours (GIST) after failure of imatinib.

<sup>f</sup> Non-adipocytic STS (excluding liposarcomas).

<sup>g</sup> 59% of patients had at least one previous treatment.

- **Risk factors for the disease**

Risk factors in patients with NTRK fusions are not well understood, mainly because this group of cancers are relatively rare and diverse. General risk factors for classes of cancers where NTRK fusions have been identified are provided below:

#### Adults

Risk factors that account for a high proportion of cancers worldwide where NTRK fusions have been observed are: smoking, insufficient physical activity, alcohol, diet, overweight and obesity, and infections. Other factors include familial or genetic factors, age, cardiovascular disease, respiratory diseases, diabetes, exposure to sunlight, radiation and previous cancer treatments and other cancer causing substances (WHO 2011).

#### Paediatrics

Cancer risk factors in children are not well understood, mainly because this group of cancers is relatively rare and diverse. In a small percentage (~ 5%) of childhood cancers, familial or genetic factors are thought to predispose children to cancer, and an even smaller percentage have an identified environmental link. Other risk factors that have been associated with childhood cancers include: prenatal exposure to tobacco, X-rays, or certain medications, certain medical conditions (e.g., Down syndrome), problems with development in the womb, exposure to infections, exposure to radiation and previous cancer treatments (Spector et al. 2015).

## Natural history of the indicated condition in the (untreated) population

There is no publicly available data on outcomes of patients with NTRK fusion-positive tumours. As shown in [Table 2](#), irrespective of NTRK status, prognosis for patients is poor with ORRs ranging from 0%–47.2% and median duration of responses (mDOR) ranging from 4.2–17.1 months.

- **Important co-morbidities**

Co-morbidities in patients with NTRK fusions are not well understood, mainly because this group of cancers is relatively rare and diverse. General risk factors for classes of cancers where NTRK fusions have been identified are provided below:

### Adults

A review of an observational study of newly diagnosed cancer patients treated at one of eight U.S. participating cancer care facilities between 1998 and 2003 showed some of the important common co-morbidities reported in adult cancer patients which include hypertension (37.7%), respiratory disease (28.5%), previous solid tumour (18.0%), angina (14.2%), diabetes (11.2%), myocardial infarction (MI [9.9%]), stroke (5.3%), congestive heart failure (CHF [5.1%]), stomach/intestinal disease (5.0%), and psychiatric disease (4.8%) ([Piccirillo et al. 2008](#)).

### Paediatrics

A diagnosis of cancer is rare and apart from high-dose radiation and prior chemotherapy there are no strong external risk factors associated with a cancer diagnosis in children as there are with adults ([Spector et al. 2015](#)). Since chronic conditions in the general paediatric population are relatively rare (common conditions in the U.S. and EU, respectively, are obesity [18% and 33%] asthma [9% and 9.4%] and attention-deficit/hyperactivity disorder [6% and 162 per 100,000] [[Perrin et al. 2007](#); [Selroos et al. 2015](#); [WHO 2017](#)]), there is no data available on specific co-morbidities in paediatric patients at the time of cancer diagnosis.

### Pregnancy or Breastfeeding:

Entrectinib is not intended to be used during pregnancy or breastfeeding.

## **SI.1.2 ROS1-POSITIVE, LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (please refer to approved label for full wording)**

- **Incidence**

Lung cancer remains the leading cause of cancer-related mortality worldwide. Because of low survival even in more developed countries, lung cancer mortality rates are generally similar to incidence rates. In 2018, an estimated 2.1 million new lung cancer cases were diagnosed and 1.8 million lung cancer deaths occurred ([Table 3](#)) ([IARC Lung Cancer 2018](#)). NSCLC accounts for most (>80%) lung cancer cases of which



adenocarcinoma is the most common histological subtype (Siegel et al. 2012; Howlader et al. 2016). Approximately 70% of patients with NSCLC are diagnosed with inoperable locally advanced (Stage IIIb) or metastatic (Stage IV) disease (Molina et al. 2008), for which 5-year survival rates are 5% and <1%, respectively (Silvestri et al. 2007).

**Table 3 Estimates of Lung Cancer Incidence, Mortality, and 5-year Prevalence Worldwide, in the United States, and in Europe (2018 data)**

| Country   | Incidence (N) | Incidence per 100,000 (World age-standardized rate) | Mortality (N) | Mortality per 100,000 (World age-standardized rate) | 5-year Prevalence    |
|-----------|---------------|---|---------------|---|----------------------|
| Worldwide | 2,093,876     | 22.5  | 1,761,007     | 18.6  | 2,129,964            |
| U.S.      | 227,356       | 35.1  | 152,423       | 22.1  | 255,904              |
| Europe    | 470,039       | 29.9 <sup>a</sup>                                   | 387,913       | 23.1 <sup>a</sup>                                   | 497,283 <sup>a</sup> |

n = Number of patients;

US = United States

<sup>a</sup> Average of rates from Western, Northern, Southern, and Central and Eastern Europe.

Source: IARC Lung Cancer 2018.

NSCLC has a high propensity to metastasize to the central nervous system (CNS). Brain metastases are a major clinical issue and have an adverse impact on patient morbidity and outcome. Their symptoms lead to significant impairment of quality of life and a rapid decline in the patient's clinical condition. Prognosis has historically been very poor with a median survival of 1–2 months if left untreated. Among patients with NSCLC, between 10–25% of patients with NSCLC present with CNS metastases at the time of diagnosis and up to 50% will develop CNS metastases at some point during the course of their disease (Chi and Komaki 2010; Fokas et al. 2013; Dawe et al 2014; Metro et al. 2015; Peters et al. 2017). A recent retrospective analysis comparing the presence of brain metastases and oncogene status in a group of patients with Stage IV NSCLC, investigators found no statistically significant differences in the incidence of brain metastases across ROS1, ALK, EGFR, KRAS, and BRAF or other mutations. The incidence of brain metastases in patients with treatment naïve ROS1-positive NSCLC and in patients with ALK-positive NSCLC was 36% and 34%, respectively, and it was concluded that the incidence of brain metastases does not differ from other oncogene cohorts (Patil et al. 2018).

- **Prevalence**

The overall prevalence and number of different ROS1 fusion partners (up to 14 have been described) is highest in NSCLC; however, ROS1 gene rearrangements are still rare and occur in 1%–2% of patients with NSCLC, representing a lower frequency than most other known oncogenic driver alterations in NSCLC (Takeuchi et al. 2012; Bergethon et al. 2012; Davies et al. 2012; Rimkunas et al. 2012; Stransky et al. 2014; Scheffler et al. 2015; Clavé et al. 2016).

CNS involvement in ROS1-positive NSCLC has been reported with variable incidence in several case series. Although some reports suggest its prevalence at initial metastatic diagnosis may be lower than in other NSCLC subpopulations (19% for ROS1-positive vs. 39% for ALK-positive) (Gainor et al. 2017), other reports suggest the rate is no different than the broader NSCLC population, with up to one-half of ROS1-positive NSCLC patients having CNS involvement at time of initial diagnosis (53%; Besse et al. 2017). Preliminary analysis of a cohort of ROS1-positive real world patients (n=107) from the U.S.-based Flatiron Health Network, showed that 34 patients (31.8%) had CNS metastases (unpublished data).

- **Demographics**

The median age of newly diagnosed lung cancer patients in developed countries is approximately 68 years and as many as 40% of patients may be older than 70 years at diagnosis (Bunn and Lilenbaum 2003). More than 50% of advanced NSCLC is diagnosed in patients older than 65 years (Ries et al. 2000; Havlik et al. 1994; Gridelli et al. 1997). In the last decade, the incidence and the mortality from lung cancer has decreased among individuals aged 50 years and younger, but has increased among those aged >70 years (Wingo et al. 2003). Men are more likely to develop lung cancer compared to women, although lung cancer incidence has declined more rapidly among men than in women (Henley et al. 2014). Approximately, 71% of new cases of lung cancer occur in men (Ferlay et al. 2015).

As mentioned previously, ROS1 gene rearrangements occur in 1%–2% of patients with NSCLC and similar to patients with ALK-positive NSCLC, patients with ROS1-positive NSCLC tend to be younger (median age: 50 years) and never smokers (75% of patients) with a histologic diagnosis of adenocarcinoma compared to other unselected patients with lung cancer (Gainor and Shaw 2013; Bergethon et al. 2012). There appears to no difference in prevalence among Asian and non-Asian populations (Rimkunas et al. 2012; Takeuchi et al. 2012).

- **The main existing treatment options**

Current management of NSCLC that has metastasized to the brain involves a multidisciplinary approach including supportive therapy, local therapies such as surgery, stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT), and, increasingly systemic therapy (Eichler and Loeffler 2007; Novello et al. 2016). The optimal treatment options, how to integrate systemic with local treatment modalities, and their sequence of administration, are yet to be established. Generally, clinical decision making on the therapeutic treatment approach for a particular patient takes into account prognostic factors (several scoring classifications, and more recently, nomograms have been developed [reviewed in Nieder et al. 2018]), the number of brain metastases, and individual patient preferences.

Isolated single metastatic brain lesions can be treated either by surgery and/or SRS, while SRS is the preferred treatment for two to three brain metastases. The effectiveness of these conventional local treatment options for CNS disease may be limited due to the presence of microscopic tumour foci not evident on imaging and/or distant cerebral relapse. In addition, SRS can result in acute reactions (due to cerebral edema) and chronic complications of delayed hemorrhage and radiation necrosis ([Mathieu et al. 2007](#); [Redmond et al. 2008](#)).

Whole-brain radiotherapy (WBRT) is widely used as the treatment option for patients with multiple inoperable brain metastases (i.e., >3) not amenable to surgery or radiosurgery. However, WBRT is associated with significant morbidities which include neurocognitive decline, and late delayed effects linked to radiation-induced injury. Systemic therapy, with the possibility to delay cranial radiotherapy, is considered in patients with neurologically asymptomatic brain metastases who have not received prior systemic therapy (e.g., chemotherapy, tyrosine kinase inhibitors [TKIs]) and for whom a radical and potentially curative approach (e.g., surgery, SRS) is not contemplated ([Reck et al. 2014b](#); [Novello et al. 2016](#)).

Systemic treatment options for patients with NSCLC presenting with brain metastases without molecular drivers are limited. First-line platinum-based doublet chemotherapy regimens, a standard of care for the many patients with advanced NSCLC without molecular drivers, can induce intracranial response rates in patients with brain metastases ranging from 23%–50% ([Inno et al. 2016](#)). While intracranial and systemic response rates appeared to be reasonable in these studies, chemotherapy alone has demonstrated limited survival benefit, with median overall survival ranging from 5.0 to 12.7 months in patients with advanced NSCLC and brain metastases at diagnosis ([Ali et al. 2013](#); [Inno et al. 2016](#)).

Crizotinib (XALKORI®) is the only ROS1 inhibitor currently approved indicated for the treatment of adults with ROS1-positive advanced NSCLC. Crizotinib was approved based on the results from 53 patients with ROS1-positive NSCLC in the Phase I/II study PROFILE 1001. The ORR was 70% (95% confidence interval [CI]: 56%, 82%). The median duration of response (DOR) had not been reached (95% CI: 15.2, NR), while median PFS at the time of data cut-off was 19.3 months (95% CI: 14.8, NR) ([Xalkori EU Assessment Report](#); EMEA/H/C/002489/II/0039).

Despite the clinically meaningful and durable systemic responses, there is no published information regarding the intracranial activity of crizotinib in ROS1-positive NSCLC CNS metastatic disease. The pivotal PROFILE 1001 study that led to crizotinib approval required patients with CNS disease to have all brain metastases treated or stable for 2 weeks before study entry. As such, publicly available reports of the study ([Shaw et al. 2014](#); [Xalkori EU Assessment Report](#); EMEA/H/C/002489/II/0039) make no mention of CNS involvement at study entry, and no CNS endpoints are reported. Systemic response (inclusive, but not limited to CNS disease) and PFS have been reported in an

Asian trial of crizotinib in ROS1-positive NSCLC, but this study did not specifically evaluate intracranial activity (OxOnc; [Wu et al. 2018](#)). In this trial, systemic response in patients with CNS disease at baseline was similar to that of patients without CNS disease, however there was a shorter durability of effect as assessed by systemic median PFS in patients with CNS disease at baseline compared to those without (10.2 vs. 18.8 months).

In patients with ALK-positive NSCLC, crizotinib has shown numerically lower intracranial response rates relative to systemic response (26–50% vs. 75.5%) ([Peters et al. 2017](#)). Crizotinib was also shown to have shorter median DOR for intracranial disease compared to systemic disease (3.7–5.5 vs. 11.1 months), which is likely indicative of the limited effectiveness of crizotinib in controlling CNS disease. Additionally, patients treated with crizotinib were observed to have a high incidence of CNS progression (41.4% at 12 months). A prior study had shown a similar phenomenon among patients with ALK fusion-positive NSCLC who had continued to receive crizotinib beyond progressive disease in the setting of systemic disease control, where the CNS was found to be a common site of disease progression (51%; [Ou et al. 2014](#)). This predisposition to CNS relapse may be attributable to the poor retention of crizotinib within the CNS. Cerebrospinal fluid concentrations of crizotinib have been found to be low ([Costa et al. 2011](#)) possibly due to crizotinib being a substrate of active efflux by the p-glycoprotein-1 (P-gp) transporter that is highly expressed within the blood-brain barrier ([Katayama et al. 2015](#); [Tang et al. 2014](#)).

The currently available therapies to treat patients with ROS1-positive NSCLC patients with or without metastatic CNS disease have limited efficacy and there is a need for improvement in outcomes to address this unmet medical need.

- **Risk factors for the disease**

Several of the predominant phenotypic clinicopathological characteristics associated with ROS1-positive NSCLC are shared with ALK rearrangements, such as younger age, history of never or light smoking, and adenocarcinoma histologic type ([Bergethon et al. 2012](#); [Takeuchi et al. 2012](#)); however, it should be noted that in clinical trials, ROS1 alterations have been observed across nearly all phenotypes.

Risk factors for NSCLC include cigarette smoking, second-hand or passive smoking, exposure to a number of carcinogens (radon, crystalline silica, arsenic, chrysolite asbestos, uranium etc.), high levels of air pollution ([Molina et al. 2008](#)), previous tuberculosis infection, family history of lung cancer, and previous chemotherapy or radiation treatment ([Cancer Research UK 2015](#); [National Cancer Institute: PDQ<sup>®</sup> NSCLC Treatment](#)).

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

*Mortality:* Lung cancer is the leading cause of cancer-related death worldwide, accounting for about 1.8 million cancer deaths per year, with an age-standardized mortality rate of 22.5 per 100,000 persons ([IARC Lung Cancer 2018](#)). In Europe, lung cancer is also the most common cause of cancer death, accounting for approximately 354,000 deaths in 2012, yielding a European age-standardized mortality rate of 35.2 per 100,000 persons ([European Cancer Observatory 2014](#)).

*Outcome of the untreated target disease:* Lung cancer presents as a locally advanced disease in approximately 25–30% of cases and as metastatic disease in approximately 40–50% of cases. At this stage the disease is incurable with the therapeutic options currently available ([Howlader et al. 2016](#)) and 5-year survival rate remains very poor. Although information is limited, patients with metastatic ROS1-positive NSCLC may have median survival rates of approximately 1 year without targeted therapy.

- **Important co-morbidities**

The most common co-morbidities include CHF, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD) and diabetes ([Table 4](#)) ([Edwards et al. 2014](#); [Wang et al. 2012](#)).

According to data from the Eindhoven Cancer Registry in the Netherlands, the prevalence of concomitant diseases among patients with NSCLC clearly increased with age ([Janssen-Heijnen et al. 2005](#)). Cardiovascular disease and COPD were leading comorbid conditions in older patients according to data from the Eindhoven Cancer Registry as well as a study in Spain among 320 patients with Stage IIIB/IV NSCLC ([Janssen-Heijnen et al. 2005](#); [Blanco et al. 2008](#)).

Smoking is a predominant risk factor for both COPD and lung cancer ([Grose and Milroy 2011](#)). Analysis of the Eindhoven Cancer Registry ([Van de Schans et al. 2007](#)), revealed that the prevalence of COPD was significantly higher for squamous cell lung carcinoma patients (29%) compared to those with adenocarcinoma (22%). Those with COPD were diagnosed at an earlier stage of cancer compared to those without COPD (Stage I: 31% vs. 19%, Stage II: 7% both, Stage III: 37% vs. 39% and Stage IV: 25% vs. 35%). This trend was comparable in middle-aged and elderly patients. A positive association between COPD and mortality in patients with lung cancer has been observed in several study populations ([Grose and Milroy 2011](#)).

In a prospective study of adults with arterial disease in the Netherlands, both current and former smokers with vascular disease had a significantly increased risk of lung cancer compared to persons who have never smoked. Smoking is a risk factor for both vascular disease and lung cancer, and so the observed association between these two conditions is expected ([Van Kruijsdijk et al. 2013](#)).

Entrectinib is not intended to be used during pregnancy or breastfeeding.

**Table 4 Prevalence of Selected Co-morbidities in Lung Cancer Patients Compared with People without Cancer**

| Comorbid condition          | Prevalence  |   |   |
|-----------------------------|---|---|---|
|                             | People without cancer, ≥66 years <sup>a</sup> (%) | All stages, SEER-Medicare, ≥66 years <sup>a</sup> (%) | Metastatic, U.S. VA, ≥65 years <sup>b</sup> (%) |
| Congestive heart failure    | 7   | 12  | 13  |
| COPD                        | 9   | 34  | 49  |
| Diabetes                    | 14  | 15  | 25  |
| Peripheral vascular disease | 3   | 7   | 17  |
| Cerebrovascular disease     | 5   | 7   | 13  |

COPD = chronic obstructive pulmonary disease; SEER = Surveillance, Epidemiology and End Results; VA = Department of Veterans Affairs.

<sup>a</sup> Edwards et al. 2014.

<sup>b</sup> Wang et al. 2012.

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

The toxicology program of entrectinib to date consists of oral single- and repeat-dose toxicity studies with durations up to 13 weeks in rats and dogs, up to 13-week juvenile toxicity studies in rats, in vitro and in vivo genotoxicity, embryo-fetal developmental toxicity, local tolerance (dermal and ocular), in vitro and in vivo phototoxicity studies, and battery of in vivo and in vitro safety pharmacology studies. The overall nonclinical safety data for entrectinib support the daily administration of entrectinib under close medical management of a treating physician to the targeted patient populations with advanced cancer, including paediatric patients.

### **Toxicology and Safety Pharmacology**

The main toxicities of entrectinib were observed in the CNS, skin, liver, and hematologic effects in both rats and dogs. In dogs, gastrointestinal toxicity and prolongation of QT/QTc interval were also observed. These effects were generally dose- and duration-dependent and exhibited reversibility or showed a trend toward reversibility during the recovery period. Entrectinib was not mutagenic or clastogenic and did not induce DNA damage but was found to be aneugenic in an in vitro assay. Entrectinib caused teratogenicity and embryo-fetal toxicity in rats. Apart from non-adverse decreases in prostate weights in dogs, no effects on reproductive organs were observed in repeat-dose toxicology studies. In the 13-week juvenile toxicology study, effects on CNS, skin, and hematological system as well as delays in growth and development were observed.

Key safety findings from nonclinical studies and relevance to human use are summarized in [Table 5](#).

**Table 5 Key Safety Findings from Non-Clinical Studies and Relevance to Human Use**

| Key Safety Findings   | Relevance to Human Use  |
|---|---|
| <b>Neurological Findings</b>  |   |
| <p>CNS clinical signs were observed in rats at <math>\geq 100</math> mg/kg/day (<math>C_{max} \geq 3.0</math> <math>\mu</math>M) and in dogs at <math>\geq 60</math> mg/kg/day (<math>C_{max} \geq 3.0</math> <math>\mu</math>M) in the 14-day and the 4-week (2x2 cycles) studies. In juvenile rats, CNS signs were observed at <math>\geq 8</math> mg/kg/day (<math>C_{max} \geq 0.614</math> <math>\mu</math>M). Incoordination and decreased activity were seen in adult rats, in juvenile rats non-sustained convulsions, abnormal gait, decreased activity, and tremors were observed. Dogs exhibited incoordination, staggering, abnormal gait, tremors, hypoactivity, and depression. CNS findings in rats, juvenile rats and dogs occurred at exposures equal to or greater than 1.0, 0.2, and 0.8 fold the human exposure by <math>C_{max}</math> at recommended dose, respectively. While these CNS clinical observations were associated with detection of entrectinib in the brain, there were no histopathological findings in the brain of either species. These findings were reversible.</p> | <p>Consistent with entrectinib’s CNS activity and the known association of TRK receptors’ involvement in neuronal development and maintenance of the central and peripheral nervous system, neurologic AEs have been observed in patients treated with entrectinib in clinical trials.</p> <p>A wide range of neurological AEs were observed and can be generally classified under the following categories: cognitive disorder AEs (24.2%), peripheral sensory neuropathy AEs (15.7%), dysaesthesia AEs (29.0%) ataxia AEs (15.7%), and syncope (4.6%) (Entrectinib SmPC). Most were Grade 1–2 in severity and reported less frequently in paediatric patients compared to the adult population. Overall, the type and the nature of neurological AEs observed was consistent with patient’s underlying disease or the mechanism of action of entrectinib.</p> <p>Severe neurological reactions is considered an important potential risk (see Section SVII.3.1.2.1) and are included in the Posology and method of administration (Section 4.2), Special warnings and precautions for use (Section 4.4, described as Cognitive Disorders) and Undesirable effects (Section 4.8) sections of the entrectinib SmPC.</p> |
| <b>Effects on Skin</b>  |   |
| <p>Entrectinib caused skin lesions in rats, juvenile rats and dogs at exposures <math>\geq 0.1</math> fold the human exposure by AUC at recommended dose. Skin lesions including scabs, erosions and ulcers and were dose-related. The effect was more pronounced in the rat, which occurred at doses <math>\geq 7.5</math> mg/kg/day in the 13-week study, and became dose-limiting in repeat-dose rat studies. Increases in circulating leukocyte counts, fibrinogen and serum protein levels were consistent with an inflammatory response to changes in skin. Skin findings were partially or completely reversible.</p>  | <p>Rash [basket term; includes the PTs of rash, rash maculopapular, rash pruritic, rash erythematous and rash papular] was reported in 11.5% of patients. Grade 3 and above rash occurred in 1.4% of patients (<math>q\_adr\_t\_ae\_medcon\_SE</math>); (<math>q\_smpc\_t\_ae\_medcon\_3\_SE</math>).</p> <p>Rash is included as ADR in the Undesirable effects section (Section 4.8) of the entrectinib SmPC.</p>  |

| Key Safety Findings   | Relevance to Human Use   |
|---|--|
| <b>Effects on Red Blood Cells</b>   |  |
| <p>Decreased RBC mass were observed in both species with histopathological correlates of increased extramedullary hematopoiesis in spleen and liver and changes in bone marrow. These findings were observed in rats, juvenile rats and dogs at exposures <math>\geq 0.1</math> fold the human exposure by AUC at recommended dose. These findings were either potentially due to a direct effect of entrectinib on the hematopoietic system or, secondary to entrectinib induced inflammation (skin, gastrointestinal tract) or a combination of both effects.</p> | <p>Hematologic events have been observed in patients treated with entrectinib in clinical trials. The most frequently reported hematologic toxicities were anemia and neutropenia (PTs of neutrophil count decreased and neutropenia). Anemia of all grades and Grade 3 and above were reported in 28.2% and 9.7% of patients, respectively.</p> <p>Neutropenia AEs of all grade and Grade <math>\geq 3</math> were reported in 11.3% and 4.4% of patients, respectively (<a href="#">Entrectinib SmPC</a>). Grade 3 neutropenia AEs were manageable and mostly resolved with entrectinib dose interruption, along with colony-stimulating factors in some patients. Overall, most hematologic AEs do not require intervention and/or can be generally managed with dose interruption and/reduction.</p> <p>Anemia and neutropenia are included in the Posology and method of administration (Section 4.2) and Undesirable effects (Section 4.8) sections of the entrectinib SmPC.</p> |
| <b>Gastrointestinal Effects</b>   |  |
| <p>Entrectinib caused GI effects in dogs and included dose-limiting vomiting and diarrhea, microscopically erosion/ulcer of anal squamous epithelium and/or neutrophil infiltrates in rectum were observed. These findings were observed in dogs at exposures <math>\geq 0.1</math> fold the human exposure by AUC at recommended dose.</p>   | <p>AEs of gastrointestinal disorders were a common AE observed in entrectinib clinical trials; the most common events reported (by PT) were constipation (42.9%), diarrhea (33.5%), nausea (32.1%) and vomiting (23.2%). In addition, abdominal pain (11.1%) has been observed (<a href="#">Entrectinib SmPC</a>).</p> <p>All of the events above are considered ADRs in the Undesirable effects section (Section 4.8) of the entrectinib SmPC.</p>  |
| <b>Cardiovascular System</b>  |  |
| <p>QTc prolongation was observed in dogs at exposures <math>\geq 0.1</math> fold the human exposure by <math>C_{max}</math> at recommended dose. In vitro, entrectinib inhibited hERG with an <math>IC_{50}</math> of 0.6 <math>\mu M</math> as a free drug. Increases in QT/QTc intervals were noted in repeat-dose studies at <math>\geq 15</math> mg/kg/day. No changes in QT/QTc interval were observed in single dose acute telemetry studies up to 300 mg/kg.</p>   | <p>AEs reported with PT of electrocardiogram QT prolongation have been in 10 (2.0%) patients treated with entrectinib. Of these, 5 patients experienced events of Grade 1 severity. Grade 2 and 3 events were reported in 2 and 3 patients, respectively.</p> <p>QT prolongation is considered to be important identified risk (see Section <a href="#">SVII.3.1.1.2</a>), and is included in the Posology and method of administration</p>  |



| Key Safety Findings  | Relevance to Human Use   |
|--|--|
|  | (Section 4.2), Special warnings and precautions for use (Section 4.4) and Undesirable effects (Section 4.8) sections of the entrectinib SmPC.  |
| Effects on Liver   |  |
| <p>Liver findings were observed in rats and dogs at exposures <math>\geq 0.1</math> fold the human exposure by AUC at recommended dose. Findings ranged from elevated liver weight (in rats and in dogs) to higher ALT, AST levels and total bilirubin. Histological findings observed at higher doses (<math>\geq</math>MTD) included vacuolation of hepatocytes and bile duct epithelium, and hepatocellular necrosis in rats at <math>\geq 200</math> mg/kg/day, and hepatocellular necrosis and increased pigmented macrophages at <math>\geq 60</math> mg/kg/day in dogs.</p>   | <p>The nonclinical data from two animal species at clinically relevant exposures indicate that hepatobiliary laboratory test elevations may occur in patients receiving entrectinib.</p> <p>Abnormal liver function test and liver dysfunction AEs (t_ae_aesi_SE) (Liver related investigations, signs and symptoms [SMQ], Hepatobiliary disorders [SOC]; all grade) were reported in 22.6% of patients. The most frequently reported events were laboratory abnormalities including AST increased (17.5%) and ALT increased (16.1%). The majority of liver abnormality events were Grade 1 and Grade 2, which resolved with no intervention. Overall, a larger proportion of paediatric patients experienced elevated transaminases compared to adult patients: elevated AST and ALT (51.7% and 51.7%, respectively) compared to adult patients (15.4% and 13.9%, respectively) (t_ae_inc_5P_SE).</p> <p>AST increased and ALT increased are ADRs in the Undesirable effects section (Section 4.8) of the entrectinib SmPC.</p> |
| Ocular Effects   |  |
| <p>As entrectinib was found to have phototoxic potential in an in vitro neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts [Study #1087359], a GLP in vivo phototoxicity study was conducted in Long-Evans pigmented rats at clinically relevant doses [Study #1087360]. No evidence of phototoxicity was observed in this study based the lack of conclusive skin reactions or ophthalmological and ocular histopathological evaluations. Neutrophil infiltrates in the cornea of treated animals were present with and without exposure to light and were therefore considered unrelated to phototoxicity.</p> | <p>Ocular effects have been reported as common AEs for TKIs for cancer therapy in preclinical and clinical studies (Raizman et al. 2017). In patients treated with entrectinib in clinical trials Eye disorders (by SOC) (t_ae_aesi_SE) were reported in 26.0% of patients, most frequently (<math>\geq 2\%</math> of patients) were vision blurred (8.5%), photophobia (4.2%), dry eye (3.2%), diplopia (2.6%), and eye pain (2.2%). The majority of eye disorder events were Grade 1.</p> <p>The only Grade 3 eye disorder events were diplopia reported in 2 patients, which resolved in both cases.</p> <p>Vision blurred (including diplopia, vision blurred and visual impairment) is an ADR in the Undesirable effects section (Section 4.8) of the entrectinib SmPC.</p>   |

| Key Safety Findings  | Relevance to Human Use  |
|--|---|
|  | Patients who experience these events are instructed not to drive or use machines until the symptoms resolve.  |
| Reproductive and Developmental Toxicity  |   |
| <p>Entrectinib had effects on embryo-fetal development in pregnant rats when administered from GD 6 to 17. In an embryo-fetal developmental study in rats, maternal toxicity (decreased body weight gain and food consumption) and developmental toxicities, including malformations of the brain, limbs, abdomen and spine, were observed at 200 mg/kg/day of entrectinib, approximately 2.0-fold the human exposure by AUC at the recommended dose. Lower fetal weights and reduced skeletal ossification were observed at exposures equivalent to 0.7 times the human exposure by AUC at the recommended dose. Entrectinib had no embryo-fetal developmental effect at a dose of 12.5 mg/kg/day (0.2× of human AUC at the maximum recommended human clinical dose).</p> | <p>No clinical studies assessing the reproductive and developmental toxicity of entrectinib have been conducted to date and there are currently no available data regarding the use of entrectinib during pregnancy.</p> <p>Based on animal studies, entrectinib may cause fetal harm when administered to pregnant women, therefore, embryo-fetal toxicity is included in the Fertility, pregnancy and lactation section (Section 4.6) of the entrectinib SmPC.</p> <p>Entrectinib is not intended to be used during pregnancy or breastfeeding.</p> |

| Key Safety Findings  | Relevance to Human Use  |
|--|---|
| <b>Genotoxicity</b>  |   |
| <p>Entrectinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay. Entrectinib was not clastogenic in the in vivo micronucleus assay in rats and did not induce DNA damage in comet assays in rats. A potential for abnormal chromosome segregation (aneugenicity) has been detected under in vitro conditions in cultured HPBL but not in an in vivo micronucleus assay in rats.</p>   | <p>Based on the potential for genotoxicity, male patients with female partners of child-bearing potential must use highly effective contraceptive methods during treatment and for 3 months following the last dose of entrectinib. Genotoxicity is included in the use in the Fertility, pregnancy and lactation section (Section 4.6) of the entrectinib SmPC.</p>  |
| <b>Carcinogenicity</b>   |   |
| <p>No carcinogenicity studies have been conducted with entrectinib and none are planned.</p>   | <p>Entrectinib is indicated for patients with advanced cancers; therefore, no carcinogenicity studies have been performed to establish its carcinogenic potential.</p>  |
| <b>Pediatric Effects</b>   |   |
| <p>In juvenile rat 13-week toxicology studies (dosing from PND7 to PND97 equivalent to a human neonate to age 16), effects on growth and development were observed, in addition to CNS, skin and hematological effects as seen in adult rats. The effects were seen in the dosing and recovery phases, and comprised decreased body weight gain, decreased femur length, delayed male and female sexual maturation, and deficits in neurobehavioural assessments (including functional observational battery, learning and memory). The NOAEL (4 mg/kg/day) represents 0.1 times the human exposure at the recommended adult dose based on AUC. The significance of these findings to humans is unknown.</p> | <p>The safety of entrectinib in pediatric patients has been evaluated in 29 patients with solid tumours in the CO40778 (STARTRK-NG) and GO40782 (STARTRK-2) studies. Where reported, the nature and severity of events observed in paediatrics was similar to that of the adult population.</p> <p>The incidence of the following adverse events were <math>\geq 5\%</math> higher in paediatric patients than in adults: headache, somnolence, nausea, abdominal pain, flatulence, anal incontinence, pyrexia, non-cardiac chest pain, weight increased, blood creatinine increased, AST increased, ALT increased, neutrophil count decreased, white blood cell count decreased, lymphocyte count decreased, platelet count decreased, ECG QT prolonged, GGT increased, blood phosphorus increased, blood chloride increased, muscular weakness, pain in extremity, cough, oropharyngeal pain, nasal congestion, epistaxis, rhinorrhea, tachypnoea, decreased appetite, dehydration, hypokalaemia, hyperglycaemia, hypophosphataemia, hypocalcaemia, hypernatraemia, increased appetite, hypermagnesaemia,</p> |

| Key Safety Findings | Relevance to Human Use   |
|---------------------|--|
|                     | <p>hyperphosphataemia, lung infectio<sup>n</sup>, pharyngitis, pruritus, hyperhidrosis, anaemia, photophobia, and eye pain.</p> <p>The observed safety events in the paediatric population is consistent with that observed in adults. The incidence in the paediatric population is based on a small patient population and higher frequencies in paediatric patients are often based on the small number of patients reporting the events in question.</p> <p>Neuro-developmental impairment in paediatric patients is considered an important potential risk because of findings in a juvenile rat toxicity study, which is described in the entrectinib SmPC (Section 5.3)</p> |

AE=adverse event; ADR=adverse drug reaction; ALT= alanine aminotransferase; AST= aspartate aminotransferase; AUC=area under the curve; CHF=congestive heart failure; CNS=central nervous system; GD=gestation day; GI=gastrointestinal; hERG=human ether-a-go-go-related gene; HPBL=human peripheral blood lymphocytes; MRHD= maximum recommended human clinical dose; MTD=maximum tolerated dose; NOAEL= no-observed-adverse-effect-level; PND=post-natal day; PT=Preferred term; RBC=red blood cell; SmPC=Summary of Product Characteristics; TKI=tyrosine kinase inhibitor; TRK=tropomyosin receptor kinases; UV=ultraviolet.

## **PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE**

Clinical trial exposure in the target populations is based on the following four ongoing oncology studies: ALKA-372-001 (GO40783), RXDX-101-01, RXDX-101-02 (herein referred to as GO40783 (ALKA), GO40784 (STARTRK-1), and GO40782 (STARTRK-2), respectively) in adults and RXDX-101-03 (herein referred to as CO40778 (STARTRK-NG) [Next Generation]) in young adults, adolescents and children > 4 months of age (herein referred to as the paediatric population for readability) (see [Table 6](#)).

Data have been analyzed using the integrated safety population (n=504 [[Table 6](#)]), which is defined as all patients enrolled up to 31 October 2018 in the GO40783 (ALKA), GO40784 (STARTRK-1), GO40782 (STARTRK-2), and CO40778 (STARTRK-NG) studies, who have received at least one dose of entrectinib. Data were collected up to a clinical cut-off date (CCOD) of 31 October 2018.

Data for the safety population are provided by age group (i.e., adult and paediatric), and the adult analysis sets are further divided by gene fusion status:

### Adult analysis sets

- **NTRK fusion-positive analysis set:** Patients from the GO40783 (ALKA), GO40784 (STARTRK-1) and GO40782 (STARTRK-2) studies in the safety population that have NTRK fusion-positive solid tumours (n=113).
- **ROS1-positive NSCLC analysis set:** Patients from the GO40783 (ALKA), GO40784 (STARTRK-1) and GO40782 (STARTRK-2) studies in the safety population that have ROS1-positive NSCLC (n=210).
- **Other analysis set:** Patients from the GO40783 (ALKA), GO40784 (STARTRK-1) and GO40782 (STARTRK-2) studies in the safety population with either ROS1 fusion-positive non-NSCLC, ALK fusion-positive tumours or no gene fusion identified (n=152).

### Paediatric analysis set

- **Paediatric analysis set:** Patients from the CO40778 (STARTRK-NG) and GO40782 (STARTRK-2) studies in the safety population (n=29).

The analysis datasets described above were defined by their trial enrollment; in some cases patients <18 years were enrolled in GO40782 (STARTRK-2) and patients >18 years were enrolled in CO40778 (STARTRK-NG) (see [Table 6](#) for additional details).

The dose received by patients was not the same among the Phase I and Phase II studies ([Table 6](#)). However, an integrated analysis of all studies and doses has been conducted in order to maximize exposure data, to assess the overall safety of entrectinib, regardless of the dosing regimen and length of the exposure received by the patient.

**Table 6 Overview of Studies Contributing to the Safety Population**

| <b>Study</b>                         | <b>Study Design</b>   | <b>Population</b>  | <b>Dose, Route, Regimen, and Formulation<sup>a</sup></b>  | <b>Patients Evaluable for Safety (n)</b> |
|--------------------------------------|---|--|---|--|
| ALKA-372-001 (ALKA)                  | First-In-Human, Phase I, single-arm, open-label, multicenter, dose escalation | Adult patients with advanced/metastatic solid tumours with TRKA/B/C, ROS1, or ALK genetic alterations                    | Oral, QD with F1 formulation in the following schedules:<br><u>Schedule A</u> : 100, 200, 400, 800, 1200, or 1600 mg/m <sup>2</sup> /day, 4 days on treatment and 3 days off treatment for 3 weeks followed by a 7-day rest period in 4-week cycles<br><u>Schedule B</u> : 200, 400 mg/m <sup>2</sup> /day in a continuous daily dosing regimen in 4-week cycles<br><u>Schedule C</u> : 400 or 800 mg/m <sup>2</sup> /day 4 days on treatment and 3 days off treatment in 4-week cycles | 60                                       |
| RXDX-101-01 (STARTRK-1)              | Phase I, single-arm, open-label, multicenter, dose escalation and expansion   | Adult patients with locally advanced/metastatic solid tumours with NTRK1/2/3, ROS1, or ALK molecular alterations         | Oral, QD in a continuous daily dosing regimen for 28 consecutive days:<br>– 100, 200, 400 mg/m <sup>2</sup> /day (BSA based); F1<br>– 800 mg/day (flat) F1<br>– 600 mg/day if BSA ≤ 1.85 m <sup>2</sup> F1;<br>800 mg/day if BSA > 1.85 m <sup>2</sup> F1<br>– 600 mg/day (flat) F1 and F2A   | 83                                       |
| RXDX-101-02 (STARTRK-2) <sup>b</sup> | Phase II, single-arm, open-label, multicenter                                 | Adult patients with locally advanced/metastatic solid tumours with NTRK1/2/3, ROS1, or ALK gene rearrangements (fusions) | 600 mg, F2A (4 patients received F1), Oral, QD, in a continuous daily dosing regimen in 4-week cycles   | 332 <sup>b</sup>                         |

| <b>Study</b>                          | <b>Study Design</b>   | <b>Population</b>  | <b>Dose, Route, Regimen, and Formulation<sup>a</sup></b>   | <b>Patients Evaluable for Safety (n)</b> |
|---------------------------------------|---|--|--|--|
| RXDX-101-03 (STARTRK-NG) <sup>c</sup> | Phase I/II, single-arm, open-label, dose escalation and expansion | Children, adolescents and young adults with recurrent or refractory solid tumours and primary CNS tumours, with or without TRK, ROS1, or ALK fusions | Oral, QD F1 (3 patients received F2B), in a continuous daily dosing regimen<br>Dosing as per nomogram ranging from 250 to 750 mg/m <sup>2</sup> /day | 29 <sup>bc,d</sup>                       |
| <b>Total Patients</b>                 |   |  |  | <b>504</b>                               |

ALK=Anaplastic lymphoma kinase; BSA=body surface area; CNS=central nervous system; TRK=tropomyosin receptor kinase; QD=once daily.

<sup>a</sup> F1, F2A and F2B refer to specific formulations used in the clinical development program, respectively.

<sup>b</sup> Two <sup>PPD</sup>-year old patients were enrolled in Study STARTRK-2. Details on these planned protocol deviations are provided in STARTRK-2 CSR.

For the purpose of the safety analyses presented in this report, these 2 patients have been included in the paediatric population (<18 years old)

<sup>c</sup> One <sup>PPD</sup>-year old patient and one <sup>PPD</sup>-year old patient were enrolled in Study STARTRK-NG. For the purpose of the safety analyses presented in this report, these 2 patients have been included in the adult population (≥18 years old).

<sup>d</sup> Sixteen patients were enrolled in the Phase I dose escalation and 13 additional patients were enrolled in the Phase 2 extension phase.

## Duration of Exposure

The entrectinib safety population provides data from 504 patients with 324.0 person-years of exposure (Table 7). Overall, the majority (76.4% [n=385]) of patients received treatment for <12 months, with 52.2% (n=263) receiving entrectinib for <6 months and 24.2% (n=122) for 6–12 months.

In the paediatric population, more children (62.1% [n=18]) were exposed for <6 months compared to adults (51.6% [n=245]). In addition, the paediatric population only accounted for 13.2 person-years of exposure versus 310.8 person-years seen in adults (Table 7).

## Exposure by Age and Sex

In the overall safety population, 55.0% (n=277) of patients were female and 45.0% (n=227) were male, and the majority (68.4% [n=345]) were 18–<65 years of age (Table 8). Female patients had 196.1 patient-years of exposure vs. 127.8 patient-years in male patients.

In the paediatric population, 55.2% (n=16) of patients were male and 44.8% (n=13) were female. The majority (48.3% [n=14]) of patients were 6 –<12 years of age, followed by 24.1% (n=7) aged 12–<18 years. Seven patients (24.1%) were aged between 2–<6 years of age and 1 patient (3.4%) was aged between 0 - <2 (Table 8).

## Exposure by Dose

Exposure data was calculated according to a patient's actual treatment received, and includes only the highest dose received by a patient. Overall, the majority of patients (79.6% [n=401]) received a highest dose of 600 mg of entrectinib (Table 9). In adults, the lowest dose received was 100 mg (0.2% [n=1]) and the highest was 2600 mg (0.4% [n=2]); the majority (83.6 % [n= 397]) received the indicated dose of 600 mg.

In the paediatric population, 24.1% (n=7) of patients received a dose of 400 mg, with 17.2% (n=5) and 13.8% (n=4) of patients receiving 500 mg and 700 mg, respectively. The lowest dose received was 100 mg (3.4% [n=1]) and the highest dose was 1100 mg (3.4% [n=1]) (Table 9).

## Exposure by Race

The majority of patients were White (61.5% [n=310]), followed by Asian (26.0% [n=131]), which was similar to the overall adult population (White, 59.8% [n=284]; Asian, 27.6% [n=131]). In the paediatric population, the majority (89.7% [n=26]) were also White, and the remaining 10.3% (n=3) of patients were Black or African American (Table 10).



## Table 7 Duration of Exposure

Duration of Exposure for Risk Management Plan, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

|  | ADULT-NTRK<br>(N=113) | ADULT-OTHER<br>(N=152) | ADULT-ROS1 NSCLC<br>(N=210) | ADULT-TOTAL<br>(N=475) | PEDIATRIC<br>(N=29) | TOTAL<br>(N=504) |
|--|-----------------------|------------------------|-----------------------------|------------------------|---------------------|------------------|
| Counts of Patients in Treatment duration groups  |                       |                        |                             |                        |                     |                  |
| 0 to <6 months                                   | 48 (42.5%)            | 113 (74.3%)            | 84 (40.0%)                  | 245 (51.6%)            | 18 (62.1%)          | 263 (52.2%)      |
| 6 months to <12 months                           | 37 (32.7%)            | 18 (11.8%)             | 59 (28.1%)                  | 114 (24.0%)            | 8 (27.6%)           | 122 (24.2%)      |
| 12 months to <18 months                          | 16 (14.2%)            | 11 (7.2%)              | 35 (16.7%)                  | 62 (13.1%)             | 3 (10.3%)           | 65 (12.9%)       |
| 18 months to <24 months                          | 7 (6.2%)              | 4 (2.6%)               | 19 (9.0%)                   | 30 (6.3%)              | 0                   | 30 (6.0%)        |
| >=24 months                                      | 2 (1.8%)              | 6 (3.9%)               | 13 (6.2%)                   | 21 (4.4%)              | 0                   | 21 (4.2%)        |
| Unknown  | 3 (2.7%)              | 0                      | 0                           | 3 (0.6%)               | 0                   | 3 (0.6%)         |
| Treatment duration groups in person time (years) |                       |                        |                             |                        |                     |                  |
| Total  | 73.3                  | 64.8                   | 172.6                       | 310.8                  | 13.2                | 324.0            |
| 0 to <6 months                                   | 9.8                   | 18.2                   | 19.2                        | 47.1                   | 3.2                 | 50.3             |
| 6 months to <12 months                           | 25.7                  | 12.5                   | 42.4                        | 80.6                   | 6.2                 | 86.9             |
| 12 months to <18 months                          | 20.7                  | 13.9                   | 42.6                        | 77.2                   | 3.8                 | 81.0             |
| 18 months to <24 months                          | 12.3                  | 6.4                    | 32.6                        | 51.4                   | NE                  | 51.4             |
| >=24 months                                      | 4.7                   | 13.8                   | 35.9                        | 54.5                   | NE                  | 54.5             |
| Unknown  | NE                    | NE                     | NE                          | NE                     | NE                  | NE               |

Adult patients are defined as subject >=18 years of age; Pediatric patients are defined as subjects <18 year of age  
 Person-time is defined as the sum of the exposure time (from first to last administration of study drug) for every patient.  
 NE means that there were no subjects in this exposure duration category.  
 Three GO40782 (ST02) subjects had only one dose with an unknown end date, hence the duration of exposure was unknown.

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**Table 8 Exposure by Age Group and Gender**

Extent of Exposure by Age group and Gender for Risk Management Plan, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

| Basket Group:<br>Age group (years) | No. of Patients    |                    |                    | Person Year  |              |              |
|------------------------------------|--------------------|--------------------|--------------------|--------------|--------------|--------------|
|                                    | Male               | Female             | Total              | Male         | Female       | Total        |
| <b>Total</b>                       |                    |                    |                    |              |              |              |
| 0-<2                               | 1 ( 100%)          | 0 ( 0.0%)          | 1 ( 100%)          | 0.8          | 0.0          | 0.8          |
| 2-<6                               | 1 (14.3%)          | 6 (85.7%)          | 7 ( 100%)          | 0.5          | 3.8          | 4.3          |
| 6-<12                              | 9 (64.3%)          | 5 (35.7%)          | 14 ( 100%)         | 2.5          | 2.1          | 4.6          |
| 12-<18                             | 5 (71.4%)          | 2 (28.6%)          | 7 ( 100%)          | 0.7          | 2.8          | 3.5          |
| 18-<65                             | 156 (45.2%)        | 189 (54.8%)        | 345 ( 100%)        | 94.4         | 141.1        | 235.4        |
| >=65                               | 55 (42.3%)         | 75 (57.7%)         | 130 ( 100%)        | 29.0         | 46.4         | 75.3         |
| <b>Total</b>                       | <b>227 (45.0%)</b> | <b>277 (55.0%)</b> | <b>504 ( 100%)</b> | <b>127.8</b> | <b>196.1</b> | <b>324.0</b> |
| <b>NTRK-Adult</b>                  |                    |                    |                    |              |              |              |
| 0-<2                               | 0 ( 0.0%)          | 0 ( 0.0%)          | 0 ( 0.0%)          | 0.0          | 0.0          | 0.0          |
| 2-<6                               | 0 ( 0.0%)          | 0 ( 0.0%)          | 0 ( 0.0%)          | 0.0          | 0.0          | 0.0          |
| 6-<12                              | 0 ( 0.0%)          | 0 ( 0.0%)          | 0 ( 0.0%)          | 0.0          | 0.0          | 0.0          |
| 12-<18                             | 0 ( 0.0%)          | 0 ( 0.0%)          | 0 ( 0.0%)          | 0.0          | 0.0          | 0.0          |
| 18-<65                             | 39 (51.3%)         | 37 (48.7%)         | 76 ( 100%)         | 22.4         | 26.9         | 49.4         |
| >=65                               | 16 (43.2%)         | 21 (56.8%)         | 37 ( 100%)         | 9.3          | 14.6         | 23.9         |
| <b>Total</b>                       | <b>55 (48.7%)</b>  | <b>58 (51.3%)</b>  | <b>113 ( 100%)</b> | <b>31.8</b>  | <b>41.5</b>  | <b>73.3</b>  |
| <b>ROS1 NSCLC-Adult</b>            |                    |                    |                    |              |              |              |
| 0-<2                               | 0 ( 0.0%)          | 0 ( 0.0%)          | 0 ( 0.0%)          | 0.0          | 0.0          | 0.0          |
| 2-<6                               | 0 ( 0.0%)          | 0 ( 0.0%)          | 0 ( 0.0%)          | 0.0          | 0.0          | 0.0          |
| 6-<12                              | 0 ( 0.0%)          | 0 ( 0.0%)          | 0 ( 0.0%)          | 0.0          | 0.0          | 0.0          |
| 12-<18                             | 0 ( 0.0%)          | 0 ( 0.0%)          | 0 ( 0.0%)          | 0.0          | 0.0          | 0.0          |
| 18-<65                             | 59 (38.1%)         | 96 (61.9%)         | 155 ( 100%)        | 47.3         | 89.2         | 136.5        |
| >=65                               | 21 (38.2%)         | 34 (61.8%)         | 55 ( 100%)         | 13.6         | 22.6         | 36.2         |
| <b>Total</b>                       | <b>80 (38.1%)</b>  | <b>130 (61.9%)</b> | <b>210 ( 100%)</b> | <b>60.8</b>  | <b>111.8</b> | <b>172.6</b> |

Adult patients are defined as subject>=18 years of age; Pediatric patients are defined as subjects <18 year of age

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**Table 8 Exposure by Age Group and Gender (cont.)**

Extent of Exposure by Age group and Gender for Risk Management Plan, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

| Basket Group:<br>Age group (years) | No. of Patients |             |             | Person Year |        |       |
|------------------------------------|-----------------|-------------|-------------|-------------|--------|-------|
|                                    | Male            | Female      | Total       | Male        | Female | Total |
| <b>Other-Adult</b>                 |                 |             |             |             |        |       |
| 0-<2                               | 0 ( 0.0%)       | 0 ( 0.0%)   | 0 ( 0.0%)   | 0.0         | 0.0    | 0.0   |
| 2-<6                               | 0 ( 0.0%)       | 0 ( 0.0%)   | 0 ( 0.0%)   | 0.0         | 0.0    | 0.0   |
| 6-<12                              | 0 ( 0.0%)       | 0 ( 0.0%)   | 0 ( 0.0%)   | 0.0         | 0.0    | 0.0   |
| 12-<18                             | 0 ( 0.0%)       | 0 ( 0.0%)   | 0 ( 0.0%)   | 0.0         | 0.0    | 0.0   |
| 18-<65                             | 58 (50.9%)      | 56 (49.1%)  | 114 ( 100%) | 24.7        | 24.9   | 49.6  |
| >=65                               | 18 (47.4%)      | 20 (52.6%)  | 38 ( 100%)  | 6.1         | 9.2    | 15.2  |
| Total                              | 76 (50.0%)      | 76 (50.0%)  | 152 ( 100%) | 30.7        | 34.1   | 64.8  |
| <b>Total-Adult</b>                 |                 |             |             |             |        |       |
| 0-<2                               | 0 ( 0.0%)       | 0 ( 0.0%)   | 0 ( 0.0%)   | 0.0         | 0.0    | 0.0   |
| 2-<6                               | 0 ( 0.0%)       | 0 ( 0.0%)   | 0 ( 0.0%)   | 0.0         | 0.0    | 0.0   |
| 6-<12                              | 0 ( 0.0%)       | 0 ( 0.0%)   | 0 ( 0.0%)   | 0.0         | 0.0    | 0.0   |
| 12-<18                             | 0 ( 0.0%)       | 0 ( 0.0%)   | 0 ( 0.0%)   | 0.0         | 0.0    | 0.0   |
| 18-<65                             | 156 (45.2%)     | 189 (54.8%) | 345 ( 100%) | 94.4        | 141.1  | 235.4 |
| >=65                               | 55 (42.3%)      | 75 (57.7%)  | 130 ( 100%) | 29.0        | 46.4   | 75.3  |
| Total                              | 211 (44.4%)     | 264 (55.6%) | 475 ( 100%) | 123.3       | 187.4  | 310.8 |
| <b>Pediatric</b>                   |                 |             |             |             |        |       |
| 0-<2                               | 1 ( 100%)       | 0 ( 0.0%)   | 1 ( 100%)   | 0.8         | 0.0    | 0.8   |
| 2-<6                               | 1 (14.3%)       | 6 (85.7%)   | 7 ( 100%)   | 0.5         | 3.8    | 4.3   |
| 6-<12                              | 9 (64.3%)       | 5 (35.7%)   | 14 ( 100%)  | 2.5         | 2.1    | 4.6   |
| 12-<18                             | 5 (71.4%)       | 2 (28.6%)   | 7 ( 100%)   | 0.7         | 2.8    | 3.5   |
| 18-<65                             | 0 ( 0.0%)       | 0 ( 0.0%)   | 0 ( 0.0%)   | 0.0         | 0.0    | 0.0   |
| >=65                               | 0 ( 0.0%)       | 0 ( 0.0%)   | 0 ( 0.0%)   | 0.0         | 0.0    | 0.0   |
| Total                              | 16 (55.2%)      | 13 (44.8%)  | 29 ( 100%)  | 4.5         | 8.7    | 13.2  |

Adult patients are defined as subject>=18 years of age; Pediatric patients are defined as subjects <18 year of age

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 Output: root/clinical\_studies/RO7102122/share/pool\_D120/prod/output/ah\_pr5909\_t\_ex\_rmp\_age\_SE.out  
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**Table 9 Exposure by Dose**

Exposure by Dose for Risk Management Plan, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

|   | ADULT-NTRK<br>(N=113) | ADULT-OTHER<br>(N=152) | ADULT-ROS1 NSCLC<br>(N=210) | ADULT-TOTAL<br>(N=475) | PEDIATRIC<br>(N=29) | TOTAL<br>(N=504) |
|---|-----------------------|------------------------|-----------------------------|------------------------|---------------------|------------------|
| Dose of Exposure                        |                       |                        |                             |                        |                     |                  |
| 100mg                                   | 0                     | 1 ( 0.7%)              | 0                           | 1 ( 0.2%)              | 1 ( 3.4%)           | 2 ( 0.4%)        |
| 200mg                                   | 0                     | 7 ( 4.6%)              | 0                           | 7 ( 1.5%)              | 2 ( 6.9%)           | 9 ( 1.8%)        |
| 300mg                                   | 0                     | 2 ( 1.3%)              | 0                           | 2 ( 0.4%)              | 4 (13.8%)           | 6 ( 1.2%)        |
| 350mg                                   | 0                     | 2 ( 1.3%)              | 0                           | 2 ( 0.4%)              | 0                   | 2 ( 0.4%)        |
| 400mg                                   | 0                     | 3 ( 2.0%)              | 0                           | 3 ( 0.6%)              | 7 (24.1%)           | 10 ( 2.0%)       |
| 500mg                                   | 0                     | 2 ( 1.3%)              | 0                           | 2 ( 0.4%)              | 5 (17.2%)           | 7 ( 1.4%)        |
| 600mg                                   | 109 (96.5%)           | 92 (60.5%)             | 196 (93.3%)                 | 397 (83.6%)            | 4 (13.8%)           | 401 (79.6%)      |
| 650mg                                   | 0                     | 2 ( 1.3%)              | 0                           | 2 ( 0.4%)              | 0                   | 2 ( 0.4%)        |
| 700mg                                   | 1 ( 0.9%)             | 8 ( 5.3%)              | 2 ( 1.0%)                   | 11 ( 2.3%)             | 4 (13.8%)           | 15 ( 3.0%)       |
| 750mg                                   | 0                     | 1 ( 0.7%)              | 0                           | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |
| 800mg                                   | 1 ( 0.9%)             | 18 (11.8%)             | 6 ( 2.9%)                   | 25 ( 5.3%)             | 0                   | 25 ( 5.0%)       |
| 900mg                                   | 0                     | 2 ( 1.3%)              | 0                           | 2 ( 0.4%)              | 1 ( 3.4%)           | 3 ( 0.6%)        |
| 1100mg                                  | 0                     | 1 ( 0.7%)              | 0                           | 1 ( 0.2%)              | 1 ( 3.4%)           | 2 ( 0.4%)        |
| 1200mg                                  | 1 ( 0.9%)             | 2 ( 1.3%)              | 3 ( 1.4%)                   | 6 ( 1.3%)              | 0                   | 6 ( 1.2%)        |
| 1300mg                                  | 0                     | 1 ( 0.7%)              | 1 ( 0.5%)                   | 2 ( 0.4%)              | 0                   | 2 ( 0.4%)        |
| 1400mg                                  | 0                     | 2 ( 1.3%)              | 0                           | 2 ( 0.4%)              | 0                   | 2 ( 0.4%)        |
| 1500mg                                  | 0                     | 1 ( 0.7%)              | 0                           | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |
| 1800mg                                  | 0                     | 2 ( 1.3%)              | 0                           | 2 ( 0.4%)              | 0                   | 2 ( 0.4%)        |
| 2000mg                                  | 0                     | 0                      | 1 ( 0.5%)                   | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |
| 2200mg                                  | 0                     | 2 ( 1.3%)              | 0                           | 2 ( 0.4%)              | 0                   | 2 ( 0.4%)        |
| 2400mg                                  | 1 ( 0.9%)             | 0                      | 0                           | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |
| 2600mg                                  | 0                     | 1 ( 0.7%)              | 1 ( 0.5%)                   | 2 ( 0.4%)              | 0                   | 2 ( 0.4%)        |
| Dose of Exposure in person time (years) |                       |                        |                             |                        |                     |                  |
| Total                                   | 73.3                  | 64.8                   | 172.6                       | 310.8                  | 13.2                | 324.0            |

Adult patients are defined as subject >=18 years of age; Pediatric patients are defined as subjects <18 year of age  
 n = number of patients exposed to ENTRECTINIB.  
 Person-time is defined as the sum of the exposure time (from first to last administration of study drug) for every patient.  
 NE means that there were no subjects in this exposure dose category.

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## Table 9 Exposure by Dose (cont.)

Exposure by Dose for Risk Management Plan, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

|        | ADULT-NTRK<br>(N=113) | ADULT-OTHER<br>(N=152) | ADULT-ROS1 NSCLC<br>(N=210) | ADULT-TOTAL<br>(N=475) | PEDIATRIC<br>(N=29) | TOTAL<br>(N=504) |
|--------|-----------------------|------------------------|-----------------------------|------------------------|---------------------|------------------|
| 100mg  | NE                    | 0.1                    | NE                          | 0.1                    | 0.8                 | 0.9              |
| 200mg  | NE                    | 1.0                    | NE                          | 1.0                    | 0.3                 | 1.3              |
| 300mg  | NE                    | 0.3                    | NE                          | 0.3                    | 1.9                 | 2.2              |
| 350mg  | NE                    | 0.2                    | NE                          | 0.2                    | NE                  | 0.2              |
| 400mg  | NE                    | 0.4                    | NE                          | 0.4                    | 2.7                 | 3.1              |
| 500mg  | NE                    | 0.2                    | NE                          | 0.2                    | 1.7                 | 1.9              |
| 600mg  | 69.7                  | 47.2                   | 155.0                       | 271.9                  | 1.8                 | 273.8            |
| 650mg  | NE                    | 0.1                    | NE                          | 0.1                    | NE                  | 0.1              |
| 700mg  | 0.8                   | 2.4                    | 2.5                         | 5.6                    | 2.4                 | 8.0              |
| 750mg  | NE                    | 0.2                    | NE                          | 0.2                    | NE                  | 0.2              |
| 800mg  | 1.7                   | 3.5                    | 7.3                         | 12.4                   | NE                  | 12.4             |
| 900mg  | NE                    | 0.5                    | NE                          | 0.5                    | 0.1                 | 0.7              |
| 1100mg | NE                    | 0.1                    | NE                          | 0.1                    | 1.5                 | 1.6              |
| 1200mg | 0.9                   | 0.2                    | 3.6                         | 4.7                    | NE                  | 4.7              |
| 1300mg | NE                    | 0.9                    | 1.2                         | 2.1                    | NE                  | 2.1              |
| 1400mg | NE                    | 0.3                    | NE                          | 0.3                    | NE                  | 0.3              |
| 1500mg | NE                    | 0.1                    | NE                          | 0.1                    | NE                  | 0.1              |
| 1800mg | NE                    | 3.6                    | NE                          | 3.6                    | NE                  | 3.6              |
| 2000mg | NE                    | NE                     | 3.1                         | 3.1                    | NE                  | 3.1              |
| 2200mg | NE                    | 3.2                    | NE                          | 3.2                    | NE                  | 3.2              |
| 2400mg | 0.3                   | NE                     | NE                          | 0.3                    | NE                  | 0.3              |
| 2600mg | NE                    | 0.1                    | 0.0                         | 0.2                    | NE                  | 0.2              |

Adult patients are defined as subject  $\geq 18$  years of age; Pediatric patients are defined as subjects  $< 18$  year of age  
 n = number of patients exposed to ENTRECTINIB.  
 Person-time is defined as the sum of the exposure time (from first to last administration of study drug) for every patient.  
 NE means that there were no subjects in this exposure dose category.

Program: root/clinical\_studies/RO7102122/share/pool\_D120/prod/program/ah\_pr5909\_t\_ex\_rmp.sas  
 Output: root/clinical\_studies/RO7102122/share/pool\_D120/prod/output/ah\_pr5909\_t\_ex\_rmp\_BYDOS\_SE.out  
 04SEP2019 12:58

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**Table 10 Exposure by Race**

Racial Origin for Risk Management Plan, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

|   | ADULT-NTRK<br>(N=113) | ADULT-OTHER<br>(N=152) | ADULT-ROS1 NSCLC<br>(N=210) | ADULT-TOTAL<br>(N=475) | PEDIATRIC<br>(N=29) | TOTAL<br>(N=504) |
|---|-----------------------|------------------------|-----------------------------|------------------------|---------------------|------------------|
| Counts of Patients by Race                        |                       |                        |                             |                        |                     |                  |
| Asian   | 22 (19.5%)            | 25 (16.4%)             | 84 (40.0%)                  | 131 (27.6%)            | 0                   | 131 (26.0%)      |
| Black or African American                         | 4 (3.5%)              | 6 (3.9%)               | 10 (4.8%)                   | 20 (4.2%)              | 3 (10.3%)           | 23 (4.6%)        |
| White   | 75 (66.4%)            | 109 (71.7%)            | 100 (47.6%)                 | 284 (59.8%)            | 26 (89.7%)          | 310 (61.5%)      |
| Other   | 0                     | 5 (3.3%)               | 5 (2.4%)                    | 10 (2.1%)              | 0                   | 10 (2.0%)        |
| Not reported                                      | 12 (10.6%)            | 7 (4.6%)               | 10 (4.8%)                   | 29 (6.1%)              | 0                   | 29 (5.8%)        |
| Missing #   | 0                     | 0                      | 1 (0.5%)                    | 1 (0.2%)               | 0                   | 1 (0.2%)         |
| Treatment duration in person time by Race (years) |                       |                        |                             |                        |                     |                  |
| Total   | 73.3                  | 64.8                   | 172.6                       | 310.8                  | 13.2                | 324.0            |
| Asian   | 11.5                  | 11.2                   | 56.8                        | 79.6                   | NE                  | 79.6             |
| Black or African American                         | 1.2                   | 2.6                    | 7.3                         | 11.1                   | 0.5                 | 11.6             |
| White   | 53.9                  | 48.2                   | 98.9                        | 201.0                  | 12.8                | 213.8            |
| Other   | NE                    | 0.5                    | 2.5                         | 3.0                    | NE                  | 3.0              |
| Not reported                                      | 6.7                   | 2.3                    | 6.7                         | 15.7                   | NE                  | 15.7             |
| Missing #   | NE                    | NE                     | 0.4                         | 0.4                    | NE                  | 0.4              |

Adult patients are defined as subject >=18 years of age; Pediatric patients are defined as subjects <18 year of age  
 # One patient was without race information whilst the 'Not reported' option was not selected.

Program: root/clinical\_studies/RO7102122/share/pool\_D120/prod/program/ah\_pr5909\_t\_ex\_rmp.sas  
 Output: root/clinical\_studies/RO7102122/share/pool\_D120/prod/output/ah\_pr5909\_t\_ex\_rmp\_BYRACE\_SE.out  
 04SEP2019 13:01

**PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS**

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

| <b>Criterion</b>  | <b>Reason for Exclusion</b>   | <b>Included As Missing Information? (Yes/No)</b> | <b>Rationale (if not included as missing information)</b>  |
|---|---|--|--|
| Current participation in another therapeutic clinical trial.  | Other investigational agents could confound interpretation of entrectinib safety and efficacy data.                                 | No   | Given the life-threatening nature of the proposed indications, treatment with entrectinib should be an option for such patients. No specific warning or exclusion is included in the SmPC since it is considered part of routine oncology practice to assess a patient's fitness for treatment. Entrectinib is not indicated for use in combination with any other cancer therapeutic agent. |
| Prior treatment with approved or investigational TRK, ROS1, or ALK inhibitors. Prior treatment with crizotinib was permitted in ALK- or ROS1-rearranged NSCLC patients presenting with radiographically-confirmed CNS-only progression <sup>a</sup> . | Previous treatment with other TKIs could interfere with the determination of safety or efficacy of entrectinib.                     | No   | Given the life-threatening nature of the proposed indications, treatment with entrectinib should be an option for such patients. No specific warning or exclusion is included in the SmPC since it is considered part of routine oncology practice to assess a patient's fitness for treatment.  |
| History of other previous cancer.   | Could interfere with the determination of safety or efficacy of entrectinib with respect to the qualifying solid tumour malignancy. | No   | Given the life-threatening nature of the proposed indications, treatment with entrectinib should be an option for such patients. No specific warning or exclusion is included in the SmPC since it is considered part of routine oncology practice to assess a patient's fitness for treatment.  |

| <b>Criterion</b>  | <b>Reason for Exclusion</b>   | <b>Included As Missing Information? (Yes/No)</b> | <b>Rationale (if not included as missing information)</b>   |
|---|---|--|---|
| Incomplete recovery from any surgery prior to the start of entrectinib treatment. | Could interfere with the determination of safety or efficacy of entrectinib.  | No   | No specific warning or exclusion is included in the SmPC since it is considered part of routine oncology practice to assess a patient's criteria for treatment.   |
| Patients with inadequate hepatic function.  | Unlikely to be able to tolerate entrectinib therapy.  | Yes  | See Section <a href="#">SVI13.2.1</a> for more details.   |
| Patients with inadequate renal function.  | Unlikely to be able to tolerate entrectinib therapy.  | No   | Negligible amounts of entrectinib and the active metabolite M5 are excreted unchanged in urine (~3 % of the dose) indicating renal clearance plays a minor role in the elimination of entrectinib.<br>Population PK (popPK) data obtained in patients with mild and moderate renal impairment show that the PK of entrectinib are not significantly affected in renal impairment. No formal PK study has been conducted and no popPK data was collected in patients with severe renal impairment, however, since entrectinib elimination via the kidney is negligible. Patients with renal impairment are not considered to be missing information.<br>This information has been captured adequately in the SmPC. |
| Women who are pregnant, breastfeeding or intending to become pregnant.            | To prevent inadvertent exposure to developing fetus as no fertility or pre- and post-natal development studies have been conducted.<br>It is not known whether entrectinib is excreted in human milk. | No   | Section 4.6 (Fertility, pregnancy and lactation) of the SmPC advises women of child-bearing potential to avoid pregnancy while receiving entrectinib.<br>Section 4.6 (Fertility, pregnancy and lactation) of the SmPC advises breastfeeding   |



| Criterion  | Reason for Exclusion  | Included As Missing Information? (Yes/No) | Rationale (if not included as missing information)  |
|--|---|---|---|
|  |   |   | women to discontinue breastfeed feeding during treatment with entrectinib and for 3 months after final dose.  |
| Any of the following conditions in the past 3 months: MI, unstable angina, coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, stroke, symptomatic bradycardia, or uncontrolled arrhythmias requiring medication. | To prevent exacerbation of patient's condition. Could also interfere with the determination of safety or efficacy of entrectinib.     | No  | CHF and QT prolongation are included as important identified risks (see Sections <a href="#">SVII3.1.1.1</a> and <a href="#">SVII3.1.1.2</a> , respectively).   |
| History of non-pharmacologically induced prolonged QTc interval.   | To prevent exacerbation of patient's baseline QTc interval.   | No  | QT prolongation is an important identified risk (see Section <a href="#">SVII3.1.1.2</a> ).   |
| History of additional risk factors for torsade de pointes.   | To minimize the risk of QTc prolongation in these patients.   | No  | QT prolongation is an important identified risk (see Section <a href="#">SVII3.1.1.2</a> ).   |
| Peripheral neuropathy Grade $\geq$ 2.  | TRK receptors are involved with neuronal development and maintenance; as such, central and peripheral neurologic events are expected. | No  | Given the life-threatening nature of the proposed indications, treatment with entrectinib should be an option for such patients. No specific warning or exclusion included in the SmPC since it is considered part of routine oncology practice to assess a patient's fitness for treatment. Peripheral sensory neuropathy AEs have been reported in entrectinib clinical trials. Most patients experienced events of Grade 1 or Grade 2 in severity; most of which resolved without any dose interruption and/or reduction. Few patients (1.1%) experienced Grade 3 events and all events resolved with entrectinib dose |

| <b>Criterion</b>   | <b>Reason for Exclusion</b>   | <b>Included As Missing Information? (Yes/No)</b> | <b>Rationale (if not included as missing information)</b>   |
|--|---|--|---|
|  |   |  | interruption and/or reduction. Peripheral neuropathy is an ADR in the SmPC.   |
| Known active infections (bacterial, fungal, or viral, including HIV-positive).   | Could interfere with the assessment of safety or efficacy of entrectinib.   | No   | No specific warning or exclusion included in the SmPC since it is considered part of routine oncology practice to assess a patient's fitness for treatment. Lung infection and urinary tract infections are ADRs in the SmPC.   |
| Active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes. | Could reasonably impact drug absorption.  | No   | Given the life-threatening nature of the proposed indications, treatment with entrectinib should be an option for such patients. No specific warning or exclusion included in the SmPC since it is considered part of routine oncology practice to assess a patient's criteria for treatment. |
| Known ILD, interstitial fibrosis, or history of TKI-induced pneumonitis.   | Pulmonary toxicities have been associated with tyrosine kinase inhibitors.  | No   | Given the life-threatening nature of the proposed indications, treatment with entrectinib should be an option for such patients. No specific warning or exclusion included in the SmPC since it is considered part of routine oncology practice to assess a patient's fitness for treatment.  |
| Other severe acute or chronic medical or psychiatric condition or laboratory abnormality.  | Criteria applied to ensure an efficacy analysis patient population that would generate meaningful data (e.g., without trial unrelated discontinuations) that could be statistically assessed. | No   | Severe Neurologic Reactions is an important potential risk (See Section <a href="#">SVII.3.1.2.1</a> ).   |

| Criterion  | Reason for Exclusion   | Included As Missing Information? (Yes/No) | Rationale (if not included as missing information)  |
|--|--|---|---|
| Receiving enzyme inducing antiepileptic drugs (EIAEDs) within prior 14 days. | In vitro, entrectinib inhibited the activities of CYP2C9, CYP2D6, and CYP3A4 isoforms and exhibited potential to induce CYP3A4, suggesting that drug-drug interactions are possible with entrectinib for drugs primarily metabolized by CYP3A4, CYP2C9, or CYP2D6. | No  | CYP3A4 plays a significant role in the biotransformation of entrectinib. Section 4.2 (Posology and method of administration) of the SmPC advises that co-administration of drugs that are strong or moderate CYP3A inhibitors or inducers, while taking entrectinib should be avoided. In adults, if concomitant use of strong or moderate CYP3A inhibitors cannot be avoided, dose adjustments will be required. |

AE=adverse event; ADR = adverse drug reaction; ALK = anaplastic lymphoma kinase; CHF = congestive heart failure; CNS = central nervous system; CYP: Cytochrome P450, EIAED= enzyme inducing antiepileptic drugs, HIV = human immunodeficiency virus; ILD = interstitial lung disease; MI = myocardial infarction; NSCLC=non-small cell lung cancer; PK=pharmacokinetic; QTc=corrected QT interval; SmPC = Summary of Product Characteristics; TRK = tropomyosin receptor kinase; TKI =tyrosine kinase inhibitors.

<sup>a</sup> Systemic progressors were allowed in the Phase I studies.

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

The clinical trial development program for entrectinib was unable to detect adverse drug reactions (ADRs) that are:

- **Rare adverse reactions:** The entrectinib safety population provides data from 504 patients with 324.0 patient-years of exposure from the Phase I and Phase II clinical studies GO40783 (ALKA), GO40784 (STARTRK-1), GO40782 (STARTRK-2), and CO40778 (STARTRK-NG). The number of patients exposed is insufficient to detect uncommon (frequency of  $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ) ADRs.
- **Caused by prolonged exposure (> 1 year):** Section 4.2 (Posology and method of administration) of the Entrectinib Summary of Product Characteristics (SmPC) recommends that patients are treated with entrectinib until disease progression or unacceptable toxicity. As such, the duration of treatment will vary from patient to patient. In the entrectinib integrated safety population the majority (76.4% [n=385]) of the patients were exposed for <12 months; 23.6% (n=119) of patients were exposed for >12 months (Table 7).
- **Due to cumulative effects:** In the clinical trial program, patients were treated until disease progression or unacceptable toxicity. There have been 324.0 patient-years of exposure to entrectinib through clinical trial participation (Table 7), and no cumulative toxicities have been observed to date. Section 4.2 (Posology and method of administration) of the SmPC recommends that patients are treated with entrectinib until disease progression or unacceptable toxicity. As such, the duration of treatment will vary from patient to patient.
- **Have a long latency:** This was defined as >30 days after the last treatment dose and in all studies patients were followed for 30 days after the last treatment dose. Entrectinib is used for the treatment of life-threatening disease and the impact of any safety concern with a long latency period must be considered in conjunction to the overall benefit-risk to the individual patient.
- **Have an effect on long term growth and development in the paediatric population:** For the 29 patients enrolled in the paediatric clinical trial, CO40778 (STARTRK-NG) and GO40782 (STARTRK-2) (see Part II: Module SIII), the follow-up period for AEs was for 30 days after the last dose of study drug. Overall, the paediatric population was exposed for 13.2 patient-years, with the majority exposed (75.8%) for <12 months (see Table 7 and Table 8). Entrectinib is used for the treatment of life-threatening disease and the impact of any safety concern in regard to its effect on growth and development must be considered in conjunction to the overall benefit-risk to the individual patient. Neuro-developmental impairment in paediatric patients is considered an important potential risk (see Section.SVII.3.1.2.2).

There is a potential that patients treated with entrectinib could experience ADRs that have not been previously seen within the clinical trial program. AEs in the categories described above may emerge with increasing use of entrectinib. Routine

pharmacovigilance activities are in place to monitor AEs experienced in the post-marketing setting.

### **SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS**

**Table 11 Exposure of Special Populations Included or Not in Clinical Trial Development Program**

| <b>Type of Special Population</b>   | <b>Exposure</b>  |
|---|--|
| Pregnant women  | No exposure available as not included in the clinical development program. |
| Breastfeeding women   | No exposure available as not included in the clinical development program. |
| Patients with relevant co-morbidities:<br>Patients with hepatic impairment<br>Patients with renal impairment<br>Patients with cardiovascular impairment | No exposure available as not included in the clinical development program. |
| Population with relevant different ethnic origin <sup>a</sup>   | See <a href="#">Table 10<sup>b</sup></a>                                   |
| Other: Paediatric patients  | See <a href="#">Table 8</a>  |

<sup>a</sup> All ethnicities were represented and the safety profiles are not expected to be different between ethnicities.

<sup>b</sup> Exposure by race.

## **PART II: MODULE SV – POST-AUTHORIZATION EXPERIENCE**

### **SV.1 Post-Authorization Exposure**

#### **SV.1.1 Method Used to Calculate Exposure**

Entrectinib received the marketing authorization in Japan in June 2019 and in the USA in August 2019.

**Japan:** In Japan, the product became available on the market on 04 September 2019. The number of patients exposed to entrectinib (Rozlytrek) in Japan market was estimated based on the entrectinib sales data.

**United States:** The number of patients exposed to entrectinib (Rozlytrek) in US was estimated based on milligrams of entrectinib sold. The average milligrams per patient was calculated based on average treatment duration by segment and average daily dose taking dose reductions, compliance, and persistence into account. The recommended daily dose of entrectinib in ROS1-positive metastatic NSCLC patients and NTRK + solid tumor patients is 600 mg orally once daily. The duration of therapy is informed by mPFS rate in clinical trial data. It is estimated that the compliance rate is 85% and persistence rate is 90%.

**European Economic Area (EEA) and rest of world (RoW) regions:** For EEA & RoW patient exposure estimation, indication split is used as 20% and 80% for NTRK positive and ROS1 positive, respectively.

### **SV.1.2 Exposure**

**Japan:** The estimated numbers of patients exposed in Japan (from Japan launch, 04 September 2019 to 17 June 2021) were 223 patients.

**United States:** In the reporting interval (August 2019 to June 2021), an estimated cumulative total of 610 patients have received Rozlytrek from marketing experience in US.

**EEA and RoW:** The estimated number of patients exposed in EEA were 34 patients and in RoW were 32 patients.

## **PART II: MODULE SVI – ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION**

### **POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES**

Available nonclinical and clinical data suggest that entrectinib is active within the CNS at the tested doses and administration frequency. Available AE data coded to MedDRA preferred terms (PTs) in the Food and Drug Administration (FDA) guidance for assessment of drug abuse ([CDER 2017](#)) do not show consistent patterns of occurrence (i.e., onset, duration, and resolution). The most frequently reported AEs ( $\geq 25\%$  of patients) include constipation, dysgeusia, fatigue, dizziness, diarrhea, nausea, dyspnea, edema peripheral, and anemia (t\_ae\_inc\_5P\_SE). These undesirable effects along with the inconsistent presentation of euphoric, hallucinogenic or other similar events potentially indicative of abuse are therefore unlikely to provide patients with a positive sensation that would encourage use for recreational purposes. In addition, the potential exposed population is cancer patients who would be monitored closely during their prescribed entrectinib treatment. This is in contrast to other known scheduled drugs of abuse that are intended for broader patient populations such as for the treatment of pain or other psychological conditions. Taken together, available clinical evidence does not suggest a potential for abuse with entrectinib.

### **POTENTIAL FOR MEDICATION ERRORS**

Entrectinib will be available in two capsule strengths: 200 mg capsules and 100 mg capsules. The 100 mg capsule is the preferred dose strength for paediatric patients due to capsule size and for achieving the weight-based body surface area (BSA) dosing recommendations as noted in the entrectinib SmPC.

To address the potential for medication errors regarding the appropriate dose prescribed:

- There are tables present in Section 4.2 (Posology and method of administration) in the SmPC that cover the BSA based dosing in paediatric patients.
- In addition, the two dose strengths (100mg and 200mg) of the capsules are different in terms of colour and size to differentiate the dose strengths.
  - The 100 mg capsules are yellow opaque with ENT 100 imprinted in blue on the body and presented in bottles containing 30 capsules
  - The 200 mg capsules are orange opaque with ENT 200 imprinted in blue on the body and presented in bottles containing 90 capsules

The risk mitigation is routine counseling by the health care provider to the legal guardian of the paediatric patient at the time of prescribing. The Applicant is also assessing additional modes of administration suitable for all age groups from birth:

As discussed in the Paediatric Investigation Plan, an age-appropriate formulation is under development and is planned to be evaluated in the clinical trial CO40778 (STARTRK-NG).

#### **POTENTIAL FOR OFF-LABEL USE**

Entrectinib is unlikely to be used for off-label purposes because the indication covers usage in locally advanced or metastatic solid tumours in both adult and paediatric patients with NTRK fusion-positive disease, and for ROS1-positive NSCLC. At present there is no substantial clinical data to support usage in other tumour types or malignancies outside of the indications, as the benefit-risk ratio is uncertain.

### **PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS**

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

Not applicable

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

Not Applicable.

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

### **SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks**

#### **SVII.3.1.1 Information on Important Identified Risks**

##### **SVII.3.1.1.1 Fractures**

###### **MedDRA terms:**

Bone and joint injuries (HLGT), Fractures (HLGT), Atypical Fractures Wide (Roche Standard AEGT)

###### **Potential mechanisms:**

Based on the published literature, data suggest that neurotrophins and TRK receptors may be involved in bone formation and bone remodeling processes (Su et al. 2018). TRKA was noted in animal models to be involved in local bone remodeling (Tomlinson et al. 2017). Inhibition of TRKA signaling reduced the load-induced bone formation in mice. An article describing bone remodeling in a patient treated with another NTRK inhibitor, larotrectinib, found that treatment led to significant bone healing in a 23-month old patient with tibial metastasis. The patient's metastases had led to bone destruction of the tibia, which was reversed after larotrectinib treatment (Halalsheh et al. 2018). This finding suggests that NTRK inhibition plays a role in bone homeostasis, however, it does not interfere with the development of new bone. It is not clear whether effects on TRKA inhibition may lead to an increased risk for fractures in the event of an injury in adult patients. The publications reviewed suggest that while TRKA agonism was shown to improve bone healing via osteoblast activity, there is no evidence that antagonism/inhibition would weaken the bone structure. Though these publications do not provide direct evidence of a causal relationship to fractures, there is some suggestion of a possible underlying biologic mechanism in bone maintenance.

###### **Evidence source(s) and strength of evidence:**

Evidence is based on nonclinical data (Part II: Module SII) and safety data from two Phase I/Ib studies (GO40783 [ALKA], GO40784 [STARTRK-1]), one Phase I/II study (CO40778 [STARTRK-NG]) and one Phase II study (GO40782 [STARTRK-2]) of entrectinib, in adults, adolescents, and children (n=504) with ROS1, NTRK1/2/3 or ALK alterations or fusions who received at least one dose of entrectinib (see Part II: Module SIII).

###### **Characterization of the risk:**

Of the 504 patients who received at least one dose of entrectinib in the GO40783 (ALKA), STARTRK-1, GO40782 (STARTRK-2) and CO40778 (STARTRK-NG) studies, 6.2% of patients (n=31 [95% CI: 4.22, 8.62]) experienced at least one event of fractures among which 5.3% of patients (n=25[95%CI: 3.43, 7.67]) were adults and 20.7% of patients (n=6 [95%CI: 7.99, 39.72]) were pediatric patients (Table 12). 2.4% (n=12) of



the patients experienced fractures Grade 3 in severity. Serious events were reported in 2.4% (n=12) of patients.

The incidence of all fractures by preferred term was <1%; and were most frequently leg/foot fractures. The most frequent fractures by preferred term (>0.5%, i.e., 3 or more patients) were humerus fractures and pathological fractures (4 patients each), ankle fractures, foot fractures and tibia fractures (3 patients each). Grade 3 fractures were reported in 2.4% (12/504) of patients, with pathological fractures and femoral neck fractures being the only Grade 3 events by preferred term reported in more than one patient. There were no fractures Grade  $\geq 4$ . The median time to onset of the first fractures in patients who experienced fractures was 3.4 months (range: 0.3 to 18.5 months).

None of the fractures events led to discontinuation of entrectinib. In 35.5% of cases, entrectinib dose was interrupted, but in the majority of cases no action was taken for fractures and the patient continued to receive entrectinib. At the time of the CCOD, the majority of fractures had resolved.

#### **Risk factors and risk groups:**

In adult patients, the most common cause of fractures appears to be by accidental injury. It is known that entrectinib may cause dizziness and ataxia in patients, though this seemed to be a factor in few of the falls leading to the fractures. 6.2% of patients (n=31 [95% CI: 4.22, 8.62]) experienced at least one event of fractures among which 5.3% of patients (n=25 [95% CI: 3.43, 7.67]) were adults and 20.7% of patients (n=6 [95% CI: 7.99, 39.72]) were pediatric patients.

#### **Preventability:**

Sections 4.2 and 4.4 of the SmPC provide monitoring and management guidelines to reduce the potential for negative outcomes in patients experiencing the event.

#### **Impact on the benefit-risk balance of the product:**

No patients required discontinuation of treatment with entrectinib due to fractures. Fractures events are clinically manageable and the majority of events occurring in the expanded safety population (n=504) resolved (61.3% of patient reported the outcome of the events as recovered/resolved, 12.9% – as recovering / resolving and 6.5% - as recovered / resolved with sequelae). Therefore, the impact of fractures on the benefit-risk balance of entrectinib is considered to be low.

**Public health impact:**

Fractures are isolated, clinically manageable events which are not expected to carry a significant risk to public health. The impact to public health of fractures as they relate to treatment with entrectinib is considered to be low. Informing prescribers and patients through the included warning regarding fractures in the product labeling is considered sufficient to appropriately inform and mitigate the public health impact of fractures events.

**Table 12 Fractures Seriousness, Outcomes, Severity and Frequency with 95% CI**

Adverse Events - Fractures: Seriousness, Outcomes, Severity, Frequency with 95% CI, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

Fractures

|   | NTRK-Adult<br>(N=113) | ROS1 NSCLC-Adult<br>(N=210) | Other-Adult<br>(N=152) | Total-Adult<br>(N=475) | Pediatric<br>(N=29) | Total<br>(N=504) |
|---|-----------------------|-----------------------------|------------------------|------------------------|---------------------|------------------|
| Number of Patients with Adverse Events                      | 8 (7.1%)              | 11 (5.2%)                   | 6 (3.9%)               | 25 (5.3%)              | 6 (20.7%)           | 31 (6.2%)        |
| 95% CI for Incidence Rate (Clopper-Pearson)                 | (3.11, 13.47)         | (2.64, 9.18)                | (1.46, 8.39)           | (3.43, 7.67)           | (7.99, 39.72)       | (4.22, 8.62)     |
| Overall total number of events                              | 12                    | 16                          | 7                      | 35                     | 10                  | 45               |
| No. of Patients with at least one AE by worst grade [a]     |                       |                             |                        |                        |                     |                  |
| Grade 1   | 2 (1.8%)              | 4 (1.9%)                    | 1 (0.7%)               | 7 (1.5%)               | 1 (3.4%)            | 8 (1.6%)         |
| Grade 2   | 2 (1.8%)              | 6 (2.9%)                    | 1 (0.7%)               | 9 (1.9%)               | 2 (6.9%)            | 11 (2.2%)        |
| Grade 3   | 4 (3.5%)              | 1 (0.5%)                    | 4 (2.6%)               | 9 (1.9%)               | 3 (10.3%)           | 12 (2.4%)        |
| No. of Patients with at least one Serious AE                | 5 (4.4%)              | 1 (0.5%)                    | 4 (2.6%)               | 10 (2.1%)              | 2 (6.9%)            | 12 (2.4%)        |
| Outcomes:   |                       |                             |                        |                        |                     |                  |
| No. of Patients with at least one AE Recovered/Resolved     | 5 (4.4%)              | 4 (1.9%)                    | 6 (3.9%)               | 15 (3.2%)              | 4 (13.8%)           | 19 (3.8%)        |
| No. of Patients with at least one AE Recovering/Resolving   | 0                     | 2 (1.0%)                    | 0                      | 2 (0.4%)               | 2 (6.9%)            | 4 (0.8%)         |
| No. of Patients with at least one AE Resolved with Sequelae | 0                     | 1 (0.5%)                    | 0                      | 1 (0.2%)               | 1 (3.4%)            | 2 (0.4%)         |
| No. of Patients with at least one AE Unresolved             | 3 (2.7%)              | 6 (2.9%)                    | 0                      | 9 (1.9%)               | 1 (3.4%)            | 10 (2.0%)        |

Adult patients are defined as subject  $\geq 18$  years of age; Pediatric patients are defined as subjects  $< 18$  year of age  
 Fracture composite terms: Ankle Fracture, Femoral Neck Fracture, Femur Fracture, Fibula Fracture, Foot Fracture, Fracture, Humerus Fracture, Jaw Fracture, Lower Limb Fracture, Pathological Fracture, Rib Fracture, Spinal Compression Fracture, Spinal Fracture, Stress Fracture, Tibia Fracture, Wrist Fracture.  
 Investigator text for AEs encoded using MedDRA version 21.1.  
 Includes AEs with start date on or after the date of first dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.  
 Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.

## Table 12 Fractures Seriousness, Outcomes, Severity and Frequency with 95% CI (cont.)

AE = adverse event; No. = number; pts = patients; CI = Confidence Interval.

Program: root/clinical\_studies/R07102122/share/pool\_D120/prod/program/q\_adr\_t\_ae\_rmp\_fra.sas  
Output: root/clinical\_studies/R07102122/share/pool\_D120/prod/output/q\_adr\_t\_ae\_rmp\_fra\_SE.out  
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### **SVII.3.1.1.2 Congestive Heart Failure**

#### **MedDRA terms:**

Cardiac failure (SMQ) - Narrow

#### **Potential mechanisms:**

The mechanism underlying CHF in entrectinib-treated patients is currently unknown. Impaired tropomyosin receptor kinase B (TRKB) signalling in the dorsal medial nucleus tractus solitarius (dmNTS) via TRKB inhibition is a theoretical mechanism by which central alterations in baroreflex sensitivity (BRS) may occur, which can result in CHF (Becker et al. 2016). CHF is characterized by numerous humoral and autonomic alterations such as an increased sympathetic nervous system tone and a desensitization of baroreflex control (Zucker et al. 2012). The physiology of baroreflex control of heart rate and sympathetic nerve activity provides an important short-term feedback loop that buffers changes to mean arterial pressure (MAP) and controls cardiac output. In CHF, alterations in BRS are indicative of dysautonomia and altered feedback control of the cardiovascular system (Goldstein et al. 1975; Zucker et al. 2009). Baroreflex desensitization in CHF is at least partly the result of central neuronal network dysfunction. The dmNTS has long been appreciated as a primary site of baroreceptor afferent termination in the CNS. TRKB signalling in the dmNTS is integral for normal baroreflex function as indicated by the blunting of baroreflex sensitivity following the antagonization of TRKB, which inhibited baroreflex gain and range.

Another potential mechanism is the accumulation and redistribution of body fluid with the expansion over time of the interstitial and intravascular compartments often ultimately leading to volume overload and organ congestion. The renal retention of sodium and water is an early response mechanism contributing to fluid accumulation, but redistribution of fluid mainly from abdominal venous reservoir secondary to changes in venous capacitance to the central cardiopulmonary vascular beds is also a significant factor in the development of acute and subacute symptom progression and clinical congestion (Miller 2016).

#### **Evidence source(s) and strength of evidence:**

Evidence is based on the safety data from two Phase I/Ib studies (GO40783 [ALKA], GO40784 [STARTRK-1]), one Phase I/II study (CO40778 [STARTRK-NG]) and one Phase II study (GO40782 [STARTRK-2]) of entrectinib, in adults, adolescents, and children (n=504) with, ROS1, NTRK1/2/3 or ALK alterations or fusions who received at least one dose of entrectinib (see Part II: Module SIII).

#### **Characterization of the risk:**

Of the 504 patients who received at least one dose of entrectinib in the GO40783 (ALKA), GO40784 (GO40784 [STARTRK-1]), GO40782 [STARTRK-2] and CO40778 [STARTRK-NG] studies, 3.2% of patients (n=16 [95% CI: 1.83, 5.10]) experienced at least one event of CHF (Table 13). 2.0% (n=10), 0.2% (n=1) and 0.2% (n=1) of the

patients experienced symptomatic CHF events Grade 3, Grade 4 and Grade 5, respectively in severity. Serious events were reported in 1.8% (n=9) of patients.

One Grade 5 event of cardiogenic shock due to pericardial effusion and pericardial tamponade was reported in a patient 2 days after starting entrectinib. Upon medical review, the nature and clinical course of the event was not consistent with CHF, and the event was considered unrelated to entrectinib by the investigator. Due to the search criteria used for the RMP, “Cardiac failure (SMQ) – Narrow”, the event is included in [Table 13](#).

Of the remaining 15 patients with CHF events, 7 patients had past medical cardiac history at baseline and/or concurrent conditions that may have predisposed them to CHF. Overall, CHF events were observed in patients with or without other cardiac history and most events resolved with diuretics, entrectinib dose interruption and/or reduction. At the time of the CCOD, 0.6% (n=3) of patients had at least one event that was unresolved ([Table 13](#)).

Monitoring and management of CHF should minimize the impact on the patient’s quality of life.

#### **Risk factors and risk groups:**

Risk factors of heart failure include a medical history of coronary artery disease including a previous MI, age >65 years, smoking, body mass index > 27 kg/m<sup>2</sup>, sedentary life style, abnormality in lipid profile, hypertension, diabetes, atrial fibrillation, valvular heart disease, alcohol abuse, infection, and cardiomyopathy of an unknown cause ([Chargari et al. 2011](#); [National Clinical Guideline Centre 2018](#); [McMurray and Pfeffer 2005](#)).

In addition, prior cancer treatments including the most commonly used chemotherapy agents (e.g., anthracyclines, cyclophosphamide and radiation therapy) and biologic and targeted therapy drugs, can induce cardiac disorders ([Pai and Nahata 2000](#); [Vallebona 2000](#); [Tiersten et al. 2004](#)).

#### **Preventability:**

Patients receiving entrectinib should be carefully monitored for clinical signs and symptoms of CHF, including shortness of breath or edema, should be evaluated and treated as clinically appropriate. Based on the severity of the CHF event, treatment with entrectinib should be withheld and resumed at a reduced dose or discontinued.

Treatment should address contributing factors (e.g., hypertension, myocardial ischemia or infarction, diabetes mellitus, thyroid dysfunction, and infection) and associated conditions ([Yancy et al. 2013](#)).

Sections 4.2 and 4.4 of the SmPC provide monitoring, dose modification recommendations and management guidelines to reduce the potential for CHF.

**Impact on the benefit-risk balance of the product:**

Heart failure may manifest as asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 1) or as a symptomatic heart failure (NCI CTCAE Grade  $\geq$  2). Of the 504 patients in the entrectinib safety population, 2.0% (n=10) experienced CHF events Grade 3 in severity.

The impact on the benefit-risk balance of entrectinib is considered to be low as the incidence of CHF in patients receiving entrectinib is anticipated to be low. Careful monitoring and following of the dose management suggested in the product label further reduces the likelihood of a potential heart failure event. The current pharmacovigilance plan and product label include guidance for patient management in the event of CHF and these measures are considered adequate to manage the risk.

**Public health impact:**

From a retrospective population based study using SEER-Medicare Linked database from 1992–2005, the prevalence of CHF was 12% in patients with cancer and 7% in patients without cancer  $\geq$  66 years of age ([Edwards et al. 2014](#)). Entrectinib is intended for use in patients with locally advanced or metastatic disease and alternative treatments are also associated with cardiac toxicity. Given the low frequency of serious events, coupled with the responsiveness to dose reduction, interruption and/or treatment with diuretics, the impact of CHF on public health is considered to be low.

**Table 13 Congestive Heart Failure: Seriousness, Outcomes, Severity and Frequency with 95% CI**

Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

Congestive Heart Failure

|  | NTRK-Adult<br>(N=113) | ROS1 NSCLC-Adult<br>(N=210) | Other-Adult<br>(N=152) | Total-Adult<br>(N=475) | Pediatric<br>(N=29) | Total<br>(N=504) |
|--|-----------------------|-----------------------------|------------------------|------------------------|---------------------|------------------|
| Number of Patients with Adverse Events                         | 3 ( 2.7%)             | 7 ( 3.3%)                   | 5 ( 3.3%)              | 15 ( 3.2%)             | 1 (3.4%)            | 16 ( 3.2%)       |
| 95% CI for Incidence Rate (Clopper-Pearson)                    | (0.55, 7.56)          | (1.35, 6.75)                | (1.08, 7.51)           | (1.78, 5.16)           | (0.09, 17.76)       | (1.83, 5.10)     |
| Overall total number of events                                 | 7                     | 9                           | 8                      | 24                     | 7                   | 31               |
| No. of Patients with at least one AE by worst grade [a]        |                       |                             |                        |                        |                     |                  |
| Grade 1  | 0                     | 1 ( 0.5%)                   | 0                      | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |
| Grade 2  | 0                     | 1 ( 0.5%)                   | 2 ( 1.3%)              | 3 ( 0.6%)              | 0                   | 3 ( 0.6%)        |
| Grade 3  | 3 ( 2.7%)             | 4 ( 1.9%)                   | 3 ( 2.0%)              | 10 ( 2.1%)             | 0                   | 10 ( 2.0%)       |
| Grade 4  | 0                     | 0                           | 0                      | 0                      | 1 (3.4%)            | 1 ( 0.2%)        |
| Grade 5  | 0                     | 1 ( 0.5%)                   | 0                      | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |
| No. of Patients with at least one Serious AE                   | 2 ( 1.8%)             | 4 ( 1.9%)                   | 2 ( 1.3%)              | 8 ( 1.7%)              | 1 (3.4%)            | 9 ( 1.8%)        |
| Outcomes:  |                       |                             |                        |                        |                     |                  |
| No. of Patients with at least one AE resulted in Fatal outcome | 0                     | 1 ( 0.5%)                   | 0                      | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |
| No. of Patients with at least one AE Recovered/Resolved        | 3 ( 2.7%)             | 4 ( 1.9%)                   | 4 ( 2.6%)              | 11 ( 2.3%)             | 1 (3.4%)            | 12 ( 2.4%)       |
| No. of Patients with at least one AE Resolved with Sequelae    | 0                     | 1 ( 0.5%)                   | 0                      | 1 ( 0.2%)              | 1 (3.4%)            | 2 ( 0.4%)        |
| No. of Patients with at least one AE Unresolved                | 0                     | 2 ( 1.0%)                   | 1 ( 0.7%)              | 3 ( 0.6%)              | 0                   | 3 ( 0.6%)        |

Adult patients are defined as subject >=18 years of age; Pediatric patients are defined as subjects <18 year of age

Investigator text for AEs encoded using MedDRA version 21.1.

Includes AEs with start date on or after the date of first dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.

Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.

AE = adverse event; No. = number; pts = patients; CI = Confidence Interval.

Program: root/clinical\_studies/RO7102122/share/pool\_D120/prod/program/ah\_pr5909\_t\_ae\_rmp.sas

Output: root/clinical\_studies/RO7102122/share/pool\_D120/prod/output/ah\_pr5909\_t\_ae\_rmp\_SE.out

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Note: Based on medical review of the nature and clinical course of the event the Grade 5 event of cardiogenic shock was considered not consistent with CHF.



### SVII.3.1.1.3 QT Prolongation

#### MedDRA terms:

Torsade de pointes/QT prolongation (SMQ) - Narrow

#### Potential mechanisms:

For entrectinib, hERG data ( $IC_{50}=0.6 \mu\text{M}$ ) indicate a potential liability for QT prolongation at a 30-fold multiple to unbound human mean  $C_{\text{max,ss}}$  ( $0.018 \mu\text{M}$ ). However, QTc prolongation was not seen after acute high dosing in dogs (300 mg/kg) but only after multiple dosing at dose levels as low as 15 mg/kg/day with calculated unbound exposures of  $\sim 0.002 \mu\text{M}$  (300-fold below hERG  $IC_{50}$ ). This indicates a potential mechanism for QT prolongation other than direct hERG block (see [Part II: Module SII](#)). Of note, TKIs are associated with prolongation of the QTc interval on the electrocardiogram (ECG) ([Shah et al. 2013](#)). A defined mechanism to explain the QT-prolonging effects of entrectinib is unknown; however, a plausible hypothesis is that the three-dimensional structural configurations of TKIs uniquely interact with hERG potassium current resulting in QT prolongation. Classes of molecularly targeted agents with described QT effects include histone deacetylase inhibitors, multi-targeted TKIs, vascular disruption agents, farnesyl protein transferase inhibitors, Src/Abl kinase inhibitors, and protein kinase C inhibitors ([Strevel et al. 2007](#)).

#### Evidence source(s) and strength of evidence:

Evidence is based on nonclinical data ([Part II: Module SII](#)) and safety data from two Phase I/Ib studies (GO40783 [ALKA], GO40784 [STARTRK-1]), one Phase I/II study (CO40778 [STARTRK-NG]) and one Phase II study (GO40782 [STARTRK-2]) of entrectinib, in adults, adolescents, and children ( $n=504$ ) with, ROS1, NTRK1/2/3 or ALK alterations or fusions who received at least one dose of entrectinib (see [Part II: Module SIII](#)).

#### Characterization of the risk:

Of the 504 patients who received at least one dose of entrectinib in the GO40783 [ALKA], GO40784 [STARTRK-1], GO40782 [STARTRK-2] and CO40778 [STARTRK-NG] studies, 2.0% of patients ( $n=10$  [95% CI: 0.96, 3.62]) experienced at least one event of QT prolongation ([Table 14](#)). Overall, the proportion of patients with QTc interval prolongation AEs was higher in pediatric patients compared to the adult population; 2 patients (6.9%) vs. 8 patients (1.7%), respectively.

Five patients (1.0%) experienced events of Grade 1 severity. Grade 2 and Grade 3 events were reported in 2 patients (0.4%) and 3 patients (0.6%) respectively. No Grade 4 or 5 AEs were reported in the overall integrated safety population. There were no entrectinib dose interruptions or reductions for Grade 1 or 2 events, and all events except one Grade 1 event had resolved ([Table 14](#)). Five patients were asymptomatic, of these 1 patient experienced an asymptomatic Grade 3 event of electrocardiogram QT prolonged; other concurrent ECG abnormalities included premature ventricular

contractions (Grade 1) and the event resolved with entrectinib dose reduction. Two patients reported symptoms of syncope and dizziness.

In addition, intensive ECG evaluations were made in a QT sub-study of GO40782 (STARTRK-2) in patients (n=107) who received entrectinib 600 mg/day and had concentrations at date/times matching the QT assessment. Triplicate ECG recordings were made with PK sampling to allow a time-matched concentration-QT analysis. The data did not show evidence of a relationship between entrectinib or M5 concentrations and prolongation of the QT interval after correction for time effect and individual baseline QTcF value ([popPK Report 1091319](#)).

Monitoring, early identification and management of QT prolongation should adequately protect the patient from potential life-threatening outcomes, thereby minimizing the impact of these occurrences on the patient's quality of life as and if they arise.

#### **Risk factors and risk groups:**

QTc prolongation appears to occur more frequently in females. Inherited genetic polymorphisms or mutations with low penetrance, involving the same gene loci associated with phenotypically expressed long-QT syndrome, may underlie individual idiosyncrasies to the acquired form in many, if not most, cases. Some individuals have QT prolongation throughout life without any manifest arrhythmias, while others are highly susceptible to symptomatic arrhythmias, particularly torsades de pointes ([Isbister and Page 2013](#)).

Risk factors for QTc prolongation may also include patients with pre-existing conditions such as history of cardiac dysrhythmia, electrolyte disturbances, cardiac ischemia, and the concomitant use of medications with the potential to prolong QTc.

#### **Preventability:**

Treatment with entrectinib should be avoided in patients with congenital long-QT syndrome and in patients taking medications known to prolong the QT interval. Assessment of ECG at baseline and periodic monitoring of ECGs and electrolytes are recommended. Based on the severity of the QT event, treatment with entrectinib should be withheld and resumed at a reduced dose or discontinued.

Sections 4.2 and 4.4 of the SmPC provide monitoring and management guidelines to reduce the potential for negative outcomes in patients experiencing these events.

#### **Impact on the benefit-risk balance of the product:**

QTc interval prolongation increases the risk for potential life-threatening arrhythmias, however, to date no demonstrated proarrhythmic events have been observed in entrectinib clinical trials. The current pharmacovigilance plan and product label include

guidance for patient management in the event of QT prolongation and these measures are considered adequate to manage the risk.

**Public health impact:**

Since the incidence of this electrophysiologic abnormality in the general population is not known, its public health impact cannot be quantified. However, based on the available data, the rarity of cancers requiring treatment with entrectinib, the lack of demonstrated proarrhythmic events to date, and its management through monitoring and exclusion from treatment of a select group of individuals (i.e., patients with uncontrolled arrhythmia requiring medication were excluded from the clinical trial program), it is likely to have minimal public health impact.

**Table 14 QT Prolongation: Seriousness, Outcomes, Severity and Frequency with 95% CI**

Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

QT Prolongation

|   | NTRK-Adult<br>(N=113) | ROS1 NSCLC-Adult<br>(N=210) | Other-Adult<br>(N=152) | Total-Adult<br>(N=475) | Pediatric<br>(N=29) | Total<br>(N=504) |
|---|-----------------------|-----------------------------|------------------------|------------------------|---------------------|------------------|
| Number of Patients with Adverse Events                  | 0                     | 4 ( 1.9%)                   | 4 ( 2.6%)              | 8 ( 1.7%)              | 2 (6.9%)            | 10 ( 2.0%)       |
| 95% CI for Incidence Rate (Clopper-Pearson)             | (0.00, 3.21)          | (0.52, 4.80)                | (0.72, 6.60)           | (0.73, 3.29)           | (0.85, 22.77)       | (0.96, 3.62)     |
| Overall total number of events                          | NE                    | 6                           | 4                      | 10                     | 2                   | 12               |
| No. of Patients with at least one AE by worst grade [a] |                       |                             |                        |                        |                     |                  |
| Grade 1   | 0                     | 1 ( 0.5%)                   | 3 ( 2.0%)              | 4 ( 0.8%)              | 1 (3.4%)            | 5 ( 1.0%)        |
| Grade 2   | 0                     | 0                           | 1 ( 0.7%)              | 1 ( 0.2%)              | 1 (3.4%)            | 2 ( 0.4%)        |
| Grade 3   | 0                     | 3 ( 1.4%)                   | 0                      | 3 ( 0.6%)              | 0                   | 3 ( 0.6%)        |
| Outcomes:   |                       |                             |                        |                        |                     |                  |
| No. of Patients with at least one AE Recovered/Resolved | 0                     | 3 ( 1.4%)                   | 4 ( 2.6%)              | 7 ( 1.5%)              | 2 (6.9%)            | 9 ( 1.8%)        |
| No. of Patients with at least one AE Unresolved         | 0                     | 1 ( 0.5%)                   | 0                      | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |

Adult patients are defined as subject >=18 years of age; Pediatric patients are defined as subjects <18 year of age

Investigator text for AEs encoded using MedDRA version 21.1.

Includes AEs with start date on or after the date of first dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.

Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.

AE = adverse event; No. = number; pts = patients; CI = Confidence Interval.

Program: root/clinical\_studies/RO7102122/share/pool\_D120/prod/program/ah\_pr5909\_t\_ae\_rmp.sas

Output: root/clinical\_studies/RO7102122/share/pool\_D120/prod/output/ah\_pr5909\_t\_ae\_rmp\_SE.out

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## **SVII.3.1.2 Information on Important Potential Risks**

### **SVII.3.1.2.1 Severe Neurologic Reactions**

Severe neurologic reactions are defined as  $\geq$  Grade 3 neurological reactions which consists of the following MedDRA terms:

PTs of altered state of consciousness, amnesia, amnesic disorder, cognitive disorder, confusional state, delirium, disorientation, disturbance in attention, hallucination, hallucination (auditory), hallucination (visual), hallucinations (mixed), impaired reasoning, incoherent, judgement impaired, memory impairment, mental disorder, mental impairment, and mental status change.

Additional search was performed for Peripheral sensory neuropathy AEs (PTs of neuralgia, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensory neuropathy;  $\geq$  Grade 3), dysesthesias AEs (PTs of paraesthesia, hyperaesthesia, hypoaesthesia, dysaesthesia;  $\geq$  Grade 3), Ataxia AEs (PTs ataxia, balance disorder, gait disturbances;  $\geq$  Grade 3) and Seizure (by PT).

#### **Potential mechanisms:**

Mechanisms through which entrectinib causes severe neurologic reactions, including cognitive disorders are not well understood. Entrectinib is a CNS penetrant molecule that crosses the blood-brain barrier to treat both primary brain tumours and brain metastases in patients with NTRK1/2/3 (and ROS1 and ALK) fusion-positive solid tumours. It has shown brain-to-plasma concentration ratios of 0.4–2.2 in multiple animal species (mice, rats and dogs), and it also demonstrated potent anti-tumour activity in two TRKA-driven intracranial tumour models and one ALK-driven intracranial tumour model. These data are consistent with entrectinib dosing resulting in sufficient brain exposure achieving target pharmacological activities at steady-state and at clinically relevant systemic exposures which can lead to transient cognitive side effects. Furthermore, nerve growth factor (NGF), the first described neurotrophin, acts through two distinct receptors, TRKA and p75NTR. In the CNS, TRKA receptors are almost exclusively expressed in the cholinergic neurons of the cortex, septum, and basal forebrain that are implicated in spatial learning and memory. Selective TRKA activation impacts on cognition. A potential mechanism of the indirect role of TRKA in the development of cognitive disorders is hypothesized by the fact that blocking TRKA function results in withdrawal of cortical cholinergic boutons in the normal adult rat ([Debeir et al. 1999](#)) and accelerates neurodegeneration in mice with cholinergic deficits ([Capsoni et al. 2010](#)). More direct evidence is shown by the fact that cognition was restored by treatment of cognitively impaired aged rats with wild type NGF or with selective TRKA agonists ([Bruno et al. 2004](#); [Aboukassim et al. 2011](#)).

In addition, studies of loss of brain-derived neurotrophic factor (BDNF) signaling in the adult brain have led to the discovery of many roles for BDNF in the modulation of behavior. In addition to its importance in learning, studies have revealed BDNF's

involvement in cognition as well as mood-related behaviors ([Cowansage et al. 2010](#)). Long-term potentiation (LTP) is the lasting enhancement of synaptic strength between neurons and this phenomenon is considered a cellular model for associational learning and memory processes. Given the essential role of BDNF in LTP facilitation, another theoretical mechanism for cognitive disorders is the fact that blocking TRKB could result in the experimental loss of BDNF signaling leading to impaired LTP ([Patterson et al. 1996](#); [Monteggia et al. 2004](#)) and decreased learning and memory in behavioral paradigms ([Lu et al. 2008](#)).

#### **Evidence source(s) and strength of evidence:**

Evidence is based on the safety data from two Phase I/Ib studies (GO40783 [ALKA], GO40784 [STARTRK-1]), one Phase I/II study (CO40778 [STARTRK-NG]) and one Phase II study (GO40782 [STARTRK-2]) of entrectinib, in adults, adolescents, and children (n=504) with ROS1, NTRK1/2/3 or ALK alterations or fusions who received at least one dose of entrectinib (see [Part II: Module SIII](#)).

#### **Characterization of the risk:**

Of the 504 patients who received at least one dose of entrectinib in the GO40783 [ALKA], GO40784 [STARTRK-1], GO40782 [STARTRK-2] and CO40778 [STARTRK-NG] studies, 24.2% of patients (n= 122 [95% CI: 20.53, 28.19]) experienced at least one cognitive disorder event ([Table 15](#)). Overall, cognitive disorder AEs were reported less frequently in paediatric patients compared to the adult patients; 1 patient (3.4%) vs. 121 patients (25.5%), respectively.

The majority of patients (16.5% [n=83]) experienced events that were Grade 1 in severity, while 3.4% (n=17) and 4.4% (n=22) experienced events that were Grade 2 and Grade 3, respectively. Overall, 3.8% (n=19) patients experienced events that were considered to be serious. The majority of Grade 3 events were manageable and resolved with entrectinib dose interruption and/or reduction. No Grade 4 or 5 AEs of cognitive disorder were reported in the overall integrated safety population ([Table 15](#)).

Cognitive disorder AEs were reported more frequently in patients with baseline CNS metastases compared to patients without baseline CNS metastases (38.3% vs. 25.9%; [Entrectinib SmPC](#)). Cognitive AEs reported in patients with baseline CNS disease vs. patients without baseline CNS disease were: cognitive disorder (8.0% vs. 7.4%), confusional state (8.7% vs. 6.5%), disturbance in attention (2.9% vs. 6.0%), memory impairment (5.8% vs. 4.1%), amnesia (4.3% vs. 1.4%), mental status changes (4.3% vs. 0%), mental disorder (0.7% vs. 0%), hallucination (2.9% vs. 0%), and delirium (0.7% vs. 0.5%).

The impact on a patient's quality of life is dependent on the particular cognitive disorder resulting from the use of entrectinib. Confounding factors such as current illness can impact the safety monitoring, early identification and management of cognitive changes.

Peripheral sensory neuropathy AEs (PTs of neuralgia, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensory neuropathy; all grade) reported in the expanded integrated safety population were reviewed (ah\_sa1482\_t\_ae\_SE).

Most patients experienced events of Grade 1 or Grade 2 in severity that in generally were resolved without any dose interruption and/or reduction. Few patients (5 [1.0%]) experienced Grade 3 (ah\_sa1482\_t\_ae\_SE) peripheralsensory neuropathy events and all events resolved with entrectinib dose interruption and/or reduction. No Grade 4 AEs of peripheral sensory neuropathy were reported in the overall integrated safety population.

Dysesthesias AEs (PTs of paraesthesia, hyperaesthesia, hypoaesthesia, dysaesthesia; all grade) reported in the expanded integrated safety population were reviewed (ah\_sa1482\_t\_ae\_SE). Most dysesthesias AEs were of Grade 1 or Grade 2, and no Grade 4 dysesthesias AEs were reported in the overall integrated safety population. Grade 3 events of Hyperaesthesia were reported in 1 (0.2%) patient.

Ataxia AEs (PTs ataxia, balance disorder, gait disturbances; all grade) were reviewed (ah\_sa1482\_t\_ae\_SE). Most patients in the expanded safety population experienced events that were Grade 1 or Grade 2 in severity. Ataxia AEs generally resolved without any dose interruption or reduction. The frequency of Grade 3 ataxia was 0.8% and included events ataxia and gait disturbance (latter occurring in a 7 year old paediatric patient) (ah\_sa1482\_t\_ae\_34\_SE).

Adverse events of seizure (by PT) were reviewed (t\_aw\_ctc\_SE). All events were Grade 1 or 2 including one 3 –year old pediatric patient. No Grade 3 or higher events were reported. All patients experiencing seizures had either brain metastases or primary brain tumor at baseline.

### **Risk factors and risk groups:**

Patients with metastatic brain tumours can develop substantial cognitive disability, but the extent and type of cognitive dysfunction often varies from patient to patient because of differential tumour volume and location (Meyers 2000). In the entrectinib clinical trial program, 96.3% of patients had metastatic disease and 22.2% had CNS metastases at baseline per investigator assessment (Entrectinib SmPC). Chemotherapy-induced cognitive dysfunction is a common side effect and cause of morbidity in cancer patients and the majority (85.2%) of patients receiving entrectinib were previously treated with chemotherapy. Memory, attention, psychomotor function, processing speed, and executive function appear to be commonly affected (Moore 2014).

### **Preventability:**

There are currently no reliable predictors of which individual patients receiving entrectinib may be susceptible to the development of cognitive disorders. Patients

should be counseled on the potential for cognitive changes with entrectinib treatment and monitored for signs. Based on the severity of the cognitive disorder, treatment with entrectinib should be withheld and resumed at a reduced dose or discontinued.

Sections 4.2 and 4.4 of the SmPC provide monitoring and management guidelines to reduce the potential for negative outcomes in patients experiencing these events.

**Impact on the benefit-risk balance of the product:**

The impact on individual patients may differ, depending on the seriousness, severity and nature of the condition. If patients experience blurred vision, dizziness, syncope, or other cognitive events during treatment with entrectinib, they should be instructed not to drive or use machines until symptoms resolve.

The current pharmacovigilance plan and product label include guidance for patient management in the event of cognitive disorders and these measures are considered adequate to manage the risk.

**Public health impact:**

Given that the most cognitive disorder AEs were manageable and resolved with entrectinib dose interruption and/or reduction, the impact on public health is expected to be minimal and guidance for monitoring and managing cognitive disorders is provided in the product label.



**Table 15 Severe Neurological Reactions: Seriousness, Outcomes, Severity and Frequency with 95% CI**

Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

Cognitive Impairment

|   | NTRK-Adult<br>(N=113) | ROS1 NSCLC-Adult<br>(N=210) | Other-Adult<br>(N=152) | Total-Adult<br>(N=475) | Pediatric<br>(N=29) | Total<br>(N=504) |
|---|-----------------------|-----------------------------|------------------------|------------------------|---------------------|------------------|
| Number of Patients with Adverse Events                      | 21 (18.6%)            | 59 (28.1%)                  | 41 (27.0%)             | 121 (25.5%)            | 1 (3.4%)            | 122 (24.2%)      |
| 95% CI for Incidence Rate (Clopper-Pearson)                 | (11.89, 26.99)        | (22.13, 34.69)              | (20.10, 34.76)         | (21.61, 29.64)         | (0.09, 17.76)       | (20.53, 28.19)   |
| Overall total number of events                              | 28                    | 98                          | 66                     | 192                    | 1                   | 193              |
| No. of Patients with at least one AE by worst grade [a]     |                       |                             |                        |                        |                     |                  |
| Grade 1   | 15 (13.3%)            | 40 (19.0%)                  | 27 (17.8%)             | 82 (17.3%)             | 1 (3.4%)            | 83 (16.5%)       |
| Grade 2   | 1 (0.9%)              | 10 (4.8%)                   | 6 (3.9%)               | 17 (3.6%)              | 0                   | 17 (3.4%)        |
| Grade 3   | 5 (4.4%)              | 9 (4.3%)                    | 8 (5.3%)               | 22 (4.6%)              | 0                   | 22 (4.4%)        |
| No. of Patients with at least one Serious AE                | 4 (3.5%)              | 9 (4.3%)                    | 6 (3.9%)               | 19 (4.0%)              | 0                   | 19 (3.8%)        |
| Outcomes:   |                       |                             |                        |                        |                     |                  |
| No. of Patients with at least one AE Recovered/Resolved     | 11 (9.7%)             | 34 (16.2%)                  | 29 (19.1%)             | 74 (15.6%)             | 1 (3.4%)            | 75 (14.9%)       |
| No. of Patients with at least one AE Recovering/Resolving   | 1 (0.9%)              | 1 (0.5%)                    | 1 (0.7%)               | 3 (0.6%)               | 0                   | 3 (0.6%)         |
| No. of Patients with at least one AE Resolved with Sequelae | 1 (0.9%)              | 1 (0.5%)                    | 2 (1.3%)               | 4 (0.8%)               | 0                   | 4 (0.8%)         |
| No. of Patients with at least one AE Unresolved             | 11 (9.7%)             | 34 (16.2%)                  | 14 (9.2%)              | 59 (12.4%)             | 0                   | 59 (11.7%)       |
| No. of Patients with at least one AE with Unknown outcome   | 0                     | 0                           | 1 (0.7%)               | 1 (0.2%)               | 0                   | 1 (0.2%)         |

Adult patients are defined as subject >=18 years of age; Pediatric patients are defined as subjects <18 year of age

Investigator text for AEs encoded using MedDRA version 21.1.

Includes AEs with start date on or after the date of first dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.

Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.

AE = adverse event; No. = number; pts = patients; CI = Confidence Interval.

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### **SVII.3.1.2.2 Neuro-developmental Impairment in Paediatric Patients**

#### **MedDRA terms:**

Developmental disorders High level group term (HLGT), Cognitive and Attention Disorders and Disturbances (HLGT), Developmental disorders cognitive high level term (HLT), Intellectual disabilities (HLT), Abnormal reflexes (HLT) and Speech and language abnormalities (HLT).

#### **Potential mechanisms:**

Entrectinib is a CNS penetrant molecule that crosses the blood-brain barrier to treat both primary brain tumours and brain metastases in patients with NTRK1/2/3 (and ROS1 and ALK) fusion-positive solid tumours. It has shown brain-to-plasma concentration ratios of 0.4–2.2 in multiple animal species (mice, rats and dogs), and it also demonstrated potent anti-tumour activity in two TRKA-driven intracranial tumour models and one ALK-driven intracranial tumour model. These data are consistent with entrectinib dosing resulting in sufficient brain exposure achieving target pharmacological activities at steady-state and at clinically relevant systemic exposures which can lead to transient cognitive side effects. Furthermore, NGF, the first described neurotrophin, acts through two distinct receptors, TRKA and p75NTR. In the CNS, TRKA receptors are almost exclusively expressed in the cholinergic neurons of the cortex, septum, and basal forebrain that are implicated in spatial learning and memory. Selective TRKA activation impacts on cognition. A potential mechanism of the indirect role of TRKA in the development of cognitive disorders is hypothesized by the fact that blocking TRKA function results in withdrawal of cortical cholinergic boutons in the normal adult rat ([Debeir et al. 1999](#)) and accelerates neurodegeneration in mice with cholinergic deficits ([Capsoni et al. 2010](#)). More direct evidence is shown by the fact that cognition was restored by treatment of cognitively impaired aged rats with wild type NGF or with selective TRKA agonists ([Bruno et al. 2004](#); [Aboukassim et al. 2011](#)).

#### **Evidence source(s) and strength of evidence:**

In juvenile rat 13-week toxicology studies (dosing from PND7 to PND97 equivalent to a human neonate to age 16), effects on growth and development were observed, in addition to CNS, skin and hematological effects as seen in adult rats. The effects were seen in the dosing and recovery phases, and comprised decreased body weight gain, decreased femur length, delayed male and female sexual maturation, and deficits in neurobehavioural assessments (including functional observational battery, learning and memory). As this study represents entrectinib exposure from just after birth to age 16, it is not comparable to current experience with human exposure to entrectinib and therefore it is unknown if similar effects on neurodevelopment would result if very young children are treated with entrectinib for an extended period of time.

#### **Characterization of the risk:**

Of the 504 patients who received at least one dose of entrectinib, 29 patients were less than 18 this includes 2 patients from GO40782 (STARTRK-2) and 27 from STARTRK -

NG (93.1%) of patients); 6.9% of patients (n=2 [95% CI: 0.85, 22.77]) experienced at least one event of neuro-developmental impairment in paediatric patients (see [Table 16](#)). The reported events were aphasia (two events in one patient) and disturbance in attention (one event in one patient).

Both paediatric patients experienced events of Grade 1 severity and both the events resolved. No paediatric patient experienced developmental disorder, developmental disorder cognitive, intellectual disabilities, abnormal reflexes, speech and language abnormalities (see [Table 17](#), [Table 18](#), [Table 19](#), [Table 20](#), [Table 21](#), [Table 22](#)). Two paediatric patients (6.9%) experienced Cognitive and Attention Disorders and Disturbance of Grade 1 severity and both the events resolved.

#### **Risk factors and risk groups:**

There are no identified risk factors for neuro-developmental impairment in paediatric patients. It is unknown if age at the time of the start of treatment or if duration of treatment is correlated to neuro-developmental impairment at a later age.

#### **Preventability:**

There is limited long term exposure in paediatric patients and it is unknown if neuro-developmental impairment occurs over time or can be prevented in the paediatric population.

#### **Impact on the benefit-risk balance of the product:**

The impact on paediatric patients may differ, depending on the nature of the neuro-developmental impairment. The safety of entrectinib in paediatric patients continues to be studied in the CO40778 (STARTRK-NG) and BO41932 (TAPISTRY) studies.

#### **Public health impact:**

The impact on public health is expected to be minimal.

## Table 16 Neuro-developmental Impairment in Paediatric Patients: Seriousness, Outcomes, Severity and Frequency with 95% CI

Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI, Neuro-developmental Impairment in Pediatric Patients, Safety-Evaluable Patients  
 Protocol: CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

### Neuro-developmental Impairment in Pediatric Patients

|   | Pediatric<br>(N=29) |
|---|---------------------|
| Number of Patients with Adverse Events                  | 2 (6.9%)            |
| 95% CI for Incidence Rate (Clopper-Pearson)             | (0.85, 22.77)       |
| Overall total number of events                          | 3                   |
| No. of Patients with at least one AE by worst grade [a] |                     |
| Grade 1   | 2 (6.9%)            |
| Outcomes:   |                     |
| No. of Patients with at least one AE Recovered/Resolved | 2 (6.9%)            |

Pediatric patients are defined as subjects <18 year of age.

Investigator text for AEs encoded using MedDRA version 21.1.

Includes AEs with start date on or after the date of first dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.

Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.

AE = adverse event; No. = number; pts = patients; CI = Confidence Interval.

Neuro-developmental Impairment includes Developmental Disorder, Cognitive and Attention Disorders and Disturbance, Developmental Disorders Cognitive, Intellectual Disabilities, Abnormal Reflexes, and Speech and Language Abnormalities.

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**Table 17 Developmental Disorders in Patients: Seriousness, Outcomes, Severity and Frequency with 95% CI**

Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

Developmental Disorders

|  | NTRK-Adult<br>(N=113) | ROS1 NSCLC-Adult<br>(N=210) | Other-Adult<br>(N=152) | Total-Adult<br>(N=475) | Pediatric<br>(N=29) | Total<br>(N=504) |
|--|-----------------------|-----------------------------|------------------------|------------------------|---------------------|------------------|
| Number of Patients with Adverse Events                               | 0                     | 1 ( 0.5%)                   | 0                      | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |
| 95% CI for Incidence Rate (Clopper-Pearson)                          | (0.00, 3.21)          | (0.01, 2.62)                | (0.00, 2.40)           | (0.01, 1.17)           | (0.00, 11.94)       | (0.01, 1.10)     |
| Overall total number of events                                       | NE                    | 1                           | NE                     | 1                      | NE                  | 1                |
| No. of Patients with at least one AE by worst grade [a]<br>Grade 2   | 0                     | 1 ( 0.5%)                   | 0                      | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |
| Outcomes:<br>No. of Patients with at least one AE Recovered/Resolved | 0                     | 1 ( 0.5%)                   | 0                      | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |

Adult patients are defined as subject >=18 years of age; Pediatric patients are defined as subjects <18 year of age  
 Investigator text for AEs encoded using MedDRA version 21.1.  
 Includes AEs with start date on or after the date of first dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.  
 Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.  
 AE = adverse event; No. = number; pts = patients; CI = Confidence Interval.

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**Table 18 Cognitive and Attention Disorders and Disturbance in Patients: Seriousness, Outcomes, Severity and Frequency with 95% CI**

Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

Cognitive and Attention Disorders and Disturbance

|   | NTRK-Adult<br>(N=113) | ROS1 NSCLC-Adult<br>(N=210) | Other-Adult<br>(N=152) | Total-Adult<br>(N=475) | Pediatric<br>(N=29) | Total<br>(N=504) |
|---|-----------------------|-----------------------------|------------------------|------------------------|---------------------|------------------|
| Number of Patients with Adverse Events                      | 8 ( 7.1%)             | 25 (11.9%)                  | 19 (12.5%)             | 52 (10.9%)             | 2 (6.9%)            | 54 (10.7%)       |
| 95% CI for Incidence Rate (Clopper-Pearson)                 | (3.11, 13.47)         | (7.85, 17.07)               | (7.70, 18.83)          | (8.28, 14.11)          | (0.85, 22.77)       | (8.15, 13.75)    |
| Overall total number of events                              | 10                    | 40                          | 25                     | 75                     | 3                   | 78               |
| No. of Patients with at least one AE by worst grade [a]     |                       |                             |                        |                        |                     |                  |
| Grade 1   | 6 ( 5.3%)             | 16 ( 7.6%)                  | 13 ( 8.6%)             | 35 ( 7.4%)             | 2 (6.9%)            | 37 ( 7.3%)       |
| Grade 2   | 0                     | 7 ( 3.3%)                   | 3 ( 2.0%)              | 10 ( 2.1%)             | 0                   | 10 ( 2.0%)       |
| Grade 3   | 2 ( 1.8%)             | 2 ( 1.0%)                   | 3 ( 2.0%)              | 7 ( 1.5%)              | 0                   | 7 ( 1.4%)        |
| No. of Patients with at least one Serious AE                | 2 ( 1.8%)             | 3 ( 1.4%)                   | 2 ( 1.3%)              | 7 ( 1.5%)              | 0                   | 7 ( 1.4%)        |
| Outcomes:   |                       |                             |                        |                        |                     |                  |
| No. of Patients with at least one AE Recovered/Resolved     | 4 ( 3.5%)             | 20 ( 9.5%)                  | 12 ( 7.9%)             | 36 ( 7.6%)             | 2 (6.9%)            | 38 ( 7.5%)       |
| No. of Patients with at least one AE Recovering/Resolving   | 0                     | 1 ( 0.5%)                   | 0                      | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |
| No. of Patients with at least one AE Resolved with Sequelae | 0                     | 0                           | 1 ( 0.7%)              | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |
| No. of Patients with at least one AE Unresolved             | 5 ( 4.4%)             | 9 ( 4.3%)                   | 8 ( 5.3%)              | 22 ( 4.6%)             | 0                   | 22 ( 4.4%)       |

Adult patients are defined as subject >=18 years of age; Pediatric patients are defined as subjects <18 year of age  
 Investigator text for AEs encoded using MedDRA version 21.1.

Includes AEs with start date on or after the date of first dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.

Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.

AE = adverse event; No. = number; pts = patients; CI = Confidence Interval.

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**Table 19 Developmental Disorders Cognitive in Patients: Seriousness, Outcomes, Severity and Frequency with 95% CI**

Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

Developmental Disorders Cognitive

|   | NTRK-Adult<br>(N=113) | ROS1 NSCLC-Adult<br>(N=210) | Other-Adult<br>(N=152) | Total-Adult<br>(N=475) | Pediatric<br>(N=29) | Total<br>(N=504) |
|---|-----------------------|-----------------------------|------------------------|------------------------|---------------------|------------------|
| Number of Patients with Adverse Events      | 0                     | 0                           | 0                      | 0                      | 0                   | 0                |
| 95% CI for Incidence Rate (Clopper-Pearson) | (0.00, 3.21)          | (0.00, 1.74)                | (0.00, 2.40)           | (0.00, 0.77)           | (0.00, 11.94)       | (0.00, 0.73)     |
| Overall total number of events              | NE                    | NE                          | NE                     | NE                     | NE                  | NE               |

Adult patients are defined as subject >=18 years of age; Pediatric patients are defined as subjects <18 year of age  
 Investigator text for AEs encoded using MedDRA version 21.1.  
 Includes AEs with start date on or after the date of first dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.  
 Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.  
 AE = adverse event; No. = number; pts = patients; CI = Confidence Interval.

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## Table 20 Intellectual Disabilities in Patients: Seriousness, Outcomes, Severity and Frequency with 95% CI

Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

### Intellectual Disabilities

|   | NTRK-Adult<br>(N=113) | ROS1 NSCLC-Adult<br>(N=210) | Other-Adult<br>(N=152) | Total-Adult<br>(N=475) | Pediatric<br>(N=29) | Total<br>(N=504) |
|---|-----------------------|-----------------------------|------------------------|------------------------|---------------------|------------------|
| Number of Patients with Adverse Events      | 0                     | 0                           | 0                      | 0                      | 0                   | 0                |
| 95% CI for Incidence Rate (Clopper-Pearson) | (0.00, 3.21)          | (0.00, 1.74)                | (0.00, 2.40)           | (0.00, 0.77)           | (0.00, 11.94)       | (0.00, 0.73)     |
| Overall total number of events              | NE                    | NE                          | NE                     | NE                     | NE                  | NE               |

Adult patients are defined as subject >=18 years of age; Pediatric patients are defined as subjects <18 year of age

Investigator text for AEs encoded using MedDRA version 21.1.

Includes AEs with start date on or after the date of first dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.

Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.

AE = adverse event; No. = number; pts = patients; CI = Confidence Interval.

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**Table 21 Abnormal Reflexes in Patients: Seriousness, Outcomes, Severity and Frequency with 95% CI**

Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

Abnormal Reflexes

|   | NTRK-Adult<br>(N=113) | ROS1 NSCLC-Adult<br>(N=210) | Other-Adult<br>(N=152) | Total-Adult<br>(N=475) | Pediatric<br>(N=29) | Total<br>(N=504) |
|---|-----------------------|-----------------------------|------------------------|------------------------|---------------------|------------------|
| Number of Patients with Adverse Events      | 0                     | 0                           | 0                      | 0                      | 0                   | 0                |
| 95% CI for Incidence Rate (Clopper-Pearson) | (0.00, 3.21)          | (0.00, 1.74)                | (0.00, 2.40)           | (0.00, 0.77)           | (0.00, 11.94)       | (0.00, 0.73)     |
| Overall total number of events              | NE                    | NE                          | NE                     | NE                     | NE                  | NE               |

Adult patients are defined as subject >=18 years of age; Pediatric patients are defined as subjects <18 year of age  
 Investigator text for AEs encoded using MedDRA version 21.1.  
 Includes AEs with start date on or after the date of first dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.  
 Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.  
 AE = adverse event; No. = number; pts = patients; CI = Confidence Interval.

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**Table 22 Speech and Language Abnormalities in Patients: Seriousness, Outcomes, Severity and Frequency with 95% CI**

Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI, Safety-Evaluable Patients  
 Protocols: GO40782, GO40783, GO40784, CO40778  
 CCOD: Oct 31 2018, DBL: Dec 21 2018

Speech and Language Abnormalities

|   | NTRK-Adult<br>(N=113) | ROS1 NSCLC-Adult<br>(N=210) | Other-Adult<br>(N=152) | Total-Adult<br>(N=475) | Pediatric<br>(N=29) | Total<br>(N=504) |
|---|-----------------------|-----------------------------|------------------------|------------------------|---------------------|------------------|
| Number of Patients with Adverse Events                    | 5 ( 4.4%)             | 22 (10.5%)                  | 7 ( 4.6%)              | 34 ( 7.2%)             | 0                   | 34 ( 6.7%)       |
| 95% CI for Incidence Rate (Clopper-Pearson)               | (1.45, 10.02)         | (6.68, 15.43)               | (1.87, 9.26)           | (5.01, 9.86)           | (0.00, 11.94)       | (4.72, 9.30)     |
| Overall total number of events                            | 6                     | 29                          | 10                     | 45                     | NE                  | 45               |
| No. of Patients with at least one AE by worst grade [a]   |                       |                             |                        |                        |                     |                  |
| Grade 1   | 5 ( 4.4%)             | 14 ( 6.7%)                  | 5 ( 3.3%)              | 24 ( 5.1%)             | 0                   | 24 ( 4.8%)       |
| Grade 2   | 0                     | 6 ( 2.9%)                   | 1 ( 0.7%)              | 7 ( 1.5%)              | 0                   | 7 ( 1.4%)        |
| Grade 3   | 0                     | 2 ( 1.0%)                   | 1 ( 0.7%)              | 3 ( 0.6%)              | 0                   | 3 ( 0.6%)        |
| No. of Patients with at least one Serious AE              | 0                     | 2 ( 1.0%)                   | 0                      | 2 ( 0.4%)              | 0                   | 2 ( 0.4%)        |
| Outcomes:   |                       |                             |                        |                        |                     |                  |
| No. of Patients with at least one AE Recovered/Resolved   | 3 ( 2.7%)             | 13 ( 6.2%)                  | 3 ( 2.0%)              | 19 ( 4.0%)             | 0                   | 19 ( 3.8%)       |
| No. of Patients with at least one AE Recovering/Resolving | 0                     | 2 ( 1.0%)                   | 0                      | 2 ( 0.4%)              | 0                   | 2 ( 0.4%)        |
| No. of Patients with at least one AE Unresolved           | 2 ( 1.8%)             | 9 ( 4.3%)                   | 4 ( 2.6%)              | 15 ( 3.2%)             | 0                   | 15 ( 3.0%)       |
| No. of Patients with at least one AE with Unknown outcome | 0                     | 0                           | 1 ( 0.7%)              | 1 ( 0.2%)              | 0                   | 1 ( 0.2%)        |

Adult patients are defined as subject >=18 years of age; Pediatric patients are defined as subjects <18 year of age

Investigator text for AEs encoded using MedDRA version 21.1.

Includes AEs with start date on or after the date of first dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.

Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.

AE = adverse event; No. = number; pts = patients; CI = Confidence Interval.

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### **SVII.3.2.1 Presentation of the Missing Information**

#### **Use in patients with hepatic impairment**

##### **Evidence source:**

In vitro studies indicate that the elimination of entrectinib is predominantly through metabolism in the liver to its major active metabolite, M5, with CYP3A4 being the main isoenzyme involved in entrectinib metabolism. Furthermore, in a clinical drug-drug interaction (DDI) study, the co-administration of a strong CYP3A4 inhibitor, itraconazole, increased entrectinib exposures ( $AUC_{0-\infty}$ ) by approximately 6-fold and entrectinib exposures were decreased by approximately 77% with co-administration of a strong inducer rifampin. These results indicate that entrectinib is a sensitive substrate of CYP3A4, and that liver impairment has the potential to alter entrectinib and/or M5 exposure. No clinically significant differences in the pharmacokinetics of entrectinib were observed based on mild hepatic impairment. The impact of moderate to severe hepatic impairment on the pharmacokinetics of entrectinib is unknown.

Impaired liver function may also increase the risk of extrahepatic toxicity as elevated transaminases have been observed in the integrated safety population. Abnormal liver function test and liver dysfunction AEs ( $t_{ae\_aesi\_SE}$ ) (Liver related investigations, signs and symptoms [SMQ], Hepatobiliary disorders [SOC]; all grade) were reported in 22.6% of patients. The most frequently reported events were laboratory abnormalities including AST increased (17.5%) and ALT increased (16.1%). The majority of liver abnormality events were Grade 1 and Grade 2, which resolved with no intervention. Overall, a larger proportion of paediatric patients experienced elevated transaminases compared to adult patients: elevated AST and ALT (51.7% and 51.7%, respectively) compared to adult patients (15.4% and 13.9%, respectively) ( $t_{ae\_inc\_5P\_SE}$ ).

The safety of entrectinib in patients with hepatic impairment is not established and therefore is considered missing information.

##### **Population in need of further characterization:**

The available data are insufficient to assess the impact on the PK of entrectinib in patients with hepatic impairment and there is a need to further characterize its use in these patients.

#### **Safety in long term use**

##### **Evidence source:**

In the integrated safety population (N=504), the safety profile of entrectinib was generally comparable across all exposure groups with 261 out of 266 patients (98.1%) who were exposed to entrectinib for <6 months, all 122 patients exposed to entrectinib for 6 to <12 months, and all 116 patients exposed to entrectinib for  $\geq$ 12 months experiencing at least one AE.

**Population in need of further characterization:**

A limited number of patients have been treated with entrectinib for  $\geq 12$  months and currently the safety of entrectinib with long term exposure is not well characterized.

**PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS**

**Table 23 Summary of Safety Concerns**

| Summary of safety concerns |   |
|----------------------------|---|
| Important identified risks | <ul style="list-style-type: none"><li>• Congestive Heart Failure</li><li>• QT Prolongation</li><li>• Fractures</li></ul>                      |
| Important potential risks  | <ul style="list-style-type: none"><li>• Severe neurologic reactions</li><li>• Neuro-developmental impairment in paediatric patients</li></ul> |
| Missing information        | <ul style="list-style-type: none"><li>• Use in Patients with Hepatic Impairment</li><li>• Safety in long term use</li></ul>                   |

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

**III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES**

**Routine Pharmacovigilance Activities beyond Adverse Reactions Reporting and Signal Detection**

- Specific adverse reaction follow-up questionnaires: Not applicable.
- Other forms of routine pharmacovigilance activities: Not applicable.

**III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES**

Routine pharmacovigilance activities and ongoing and planned additional pharmacovigilance activities described in Section III.3, Table 24, are considered by the MAH/Applicant to be sufficient to obtain and analyse relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the product.

### III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

**Table 24 Ongoing and Planned Additional Pharmacovigilance Activities**

| Study Status   | Summary of Objectives   | Safety Concerns Addressed  | Milestones  | Due Date(s)               |
|--|---|--|---|---------------------------|
| <b>Category 3</b> Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA) – i.e., studies that investigate a safety concern or evaluate the effectiveness of risk-minimization activities |   |  |   |                           |
| Study GP41174<br>Ongoing   | Pharmacokinetic trial to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics and safety of Rozlytrek (entrectinib) compared to subjects with normal hepatic function  | Missing information topic 'use in patients with hepatic impairment: To determine the safety of entrectinib in patients with moderate and severe hepatic impairment, and also the impact of hepatic impairment on the pharmacokinetics of entrectinib in patients with moderate and severe hepatic impairment | Final clinical study report                                     | 31 December 2022          |
| Integrated safety analysis report to assess risk of fracture based on GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY] studies (PAESs)  | Report to characterize the risk of fractures in paediatric patients where the following bone biomarkers will be assessed: Serial assessments of BMD with DXA; bone biomarkers in blood and assessment of potential impairment of bone growth with serial hand/wrist and knee X-rays. Clinical summary of fracture events. | Risk of fractures  | Final integrated analysis report for bone biomarkers            | 31 March 2025             |
|  |   |  | Interim report will include clinical summary of fracture events | With annual re-assessment |
|  |   | Risk of fractures  | Final integrated analysis report for bone biomarkers            | 31 March 2025             |

| Study Status   | Summary of Objectives  | Safety Concerns Addressed        | Milestones  | Due Date(s)               |
|--|--|----------------------------------|---|---------------------------|
|  | Report to characterize the risk of fractures in adult patients where the following bone biomarkers will be assessed: Serial assessments of bone mineral density (BMD) with dual X-ray absorptiometry (DXA) and bone biomarkers in blood.<br>Clinical summary of fracture events. |                                  | Interim report will include clinical summary of fracture events | With annual re-assessment |
| Integrated safety analysis report to assess cardiac risks based on GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY] studies (PAESs) | Report on congestive heart failure: incidence, severity, clinical outcome and reversibility will be characterized.   | Risk of congestive heart failure | Final integrated analysis report for cardiac risks              | 30 June 2022              |
|  |  |                                  | Interim report  | With annual re-assessment |

BMD= bone mineral density; CHMP= Committee for Medicinal Products for Human Use; DXA= dual-energy x-ray absorptiometry; NCA=National Competent Authority; PAES= post-authorisation efficacy study; PRAC=Pharmacovigilance Risk Assessment Committee.

## **PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES**

Entrectinib is approved under Conditional Marketing Authorisation with the Specific Obligation to provide additional information on NTRK fusion-positive patients.

**Table 25 Planned and ongoing post-authorisation imposed efficacy studies**

| <b>Study Status</b>  | <b>Objectives</b>  | <b>Efficacy uncertainties addressed</b>              | <b>Milestones</b>                              | <b>Due Date</b>                       |
|--|--|--|--|---------------------------------------|
| <b>Efficacy studies that are conditions of the marketing authorization</b>   |  |  |  |                                       |
| Randomized, open-label, multicenter, Phase 3 study of entrectinib versus crizotinib in patients who have non-small cell lung cancer (NSCLC) harbouring ROS1 gene rearrangements with and without central nervous system metastases.<br><b>MO41552</b><br>Ongoing                           | In order to further characterise the efficacy of entrectinib in patients with baseline CNS disease, the MAH should conduct and submit the results of a randomised controlled trial versus crizotinib in treatment naïve ROS1 NSCLC patients. The primary endpoint will be PFS in the subgroup of patients with CNS metastases at baseline.   | Activity of entrectinib in patients with CNS disease | Clinical study report                          | 31 December 2027                      |
| <b>Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation</b>   |  |  |  |                                       |
| An open-label, multicenter, global Phase 2 basket study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumours that harbor NTRK1/2/3, ROS1, or ALK gene rearrangements.<br><b>RXDX-101-02</b><br><b>STARTRK-2</b><br><b>GO40782</b><br><br>Ongoing | In order to further confirm the histology-independent efficacy of entrectinib in adult and paediatric patients, the MAH should submit a pooled analysis for an increased sample size of NTRK fusion-positive patients from the ongoing studies STARTRK-2, STARTRK-NG and any additional clinical trial conducted according to an agreed protocol.<br><br>The MAH should submit the results of an interim safety and efficacy analysis of the NTRK efficacy-evaluable adult and paediatric patients including adolescents | Histology-independent efficacy in adult patients     | Interim report (SOB)<br><br>Final report (SOB) | 31 December 2023<br><br>31 March 2027 |

| Study Status   | Objectives  | Efficacy uncertainties addressed                                | Milestones  | Due Date                                     |
|--|---|---|---|--|
|  | that are available as per integrated statistical analysis plan.   |   |   |  |
| <p>A phase 1/2, open-label, dose-escalation and expansion study of entrectinib (RXDX-101) in pediatrics with locally advanced or metastatic solid or primary CNS tumors and/or who have no satisfactory treatment options.</p> <p><b>RXDX-101-03<br/>STARTRK-NG<sup>1</sup><br/>CO40778</b></p> <p>Ongoing</p>   | <p>In order to further confirm the histology-independent efficacy of entrectinib in adult and paediatric patients, the MAH should submit a pooled analysis for an increased sample size of NTRK fusion-positive patients from the ongoing studies STARTRK 2, STARTRK-NG and any additional clinical trial conducted according to an agreed protocol.</p> <p>The MAH should submit the results of an interim safety and efficacy analysis of the NTRK efficacy-evaluable adult and paediatric patients including adolescents that are available as per integrated statistical analysis plan.</p> | Histology-independent efficacy in paediatric patients           | <p>Interim report (SOB)</p> <p>Final report (SOB)</p> | <p>31 December 2023</p> <p>31 March 2027</p> |
| <p>A Phase 2, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in patients with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations or who are TMB-high as identified by a validated NGS assay. Objective of cohort B</p> | <p>In order to further confirm the histology-independent efficacy of entrectinib in adult and paediatric patients, the MAH should submit a pooled analysis for an increased sample size of NTRK fusion-positive patients from the ongoing studies STARTRK-2, STARTRK-NG and any additional clinical trial conducted according to an agreed protocol.</p> <p>The MAH should submit the results of an interim safety and efficacy analysis of the NTRK efficacy-</p>  | Histology-independent efficacy in paediatric and adult patients | <p>Interim report (SOB)</p> <p>Final report (SOB)</p> | <p>31 December 2023</p> <p>31 March 2027</p> |



| Study Status   | Objectives   | Efficacy uncertainties addressed | Milestones | Due Date |
|--|--|----------------------------------|------------|----------|
| <p>is to evaluate the efficacy of entrectinib in patients with NTRK1/2/3 fusion-positive advanced or metastatic solid tumours.</p> <p><b>TAPISTRY BO41932</b></p> <p>Ongoing</p> | <p>evaluatable adult and paediatric patients including adolescents that are available as per integrated statistical analysis plan.</p> |                                  |            |          |

ALK=Anaplastic lymphoma kinase; NTRK=neurotrophic receptor tyrosine kinase.

1. Study STARTRK-NG will continue, beyond and outside of the Specific Obligation 1 milestones, in order to fully characterize the safety concern of *Neuro-developmental impairment in paediatric patients*, with final report submission due date by 31 August 2029.

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

### **RISK-MINIMIZATION PLAN**

#### **V.1 ROUTINE RISK-MINIMIZATION MEASURES**

**Table 26 Description of Routine Risk-Minimization Measures by Safety Concern**

| Safety concern           | Routine risk-minimization activities  |
|--------------------------|---|
| Fractures                | <p><b>Routine risk communication:</b><br/>SmPC Section 4.4 – Special warnings and precautions for use<br/>SmPC Section 4.8- Undesirable effects.</p> <p><b>Routine risk-minimization activities recommending specific clinical measures to address the risk:</b><br/>Section 4.4 (Fractures) and Section 4.8 (undesirable effects) of the SmPC provide recommendations on risk management approach</p> <p><b>Other risk-minimization measures beyond the Product Information:</b><br/>None</p> <p><b>Medicine’s legal status:</b><br/>Entrectinib is a prescription only medicine</p> |
| Congestive Heart Failure | <p><b>Routine risk communication:</b><br/>SmPC Section 4.2 – Posology and Method of Administration<br/>SmPC Section 4.4 – Special warnings and precautions for use<br/>SmPC Section 4.8 – Undesirable Effects</p> <p><b>Routine risk-minimization activities recommending specific clinical measures to address the risk:</b></p>   |

| Safety concern  | Routine risk-minimization activities  |
|---|---|
|   | <p>Section 4.2 (Dose modifications), Section 4.4 (Congestive Heart Failure) and Section 4.8 (undesirable effects) of the SmPC provide recommendations on risk management approach</p> <p><b>Other risk-minimization measures beyond the Product Information:</b><br/>None</p> <p><b>Medicine's legal status:</b><br/>Entrectinib is a prescription only medicine</p>  |
| QT Prolongation                                       | <p><b>Routine risk communication:</b><br/>SmPC Section 4.2 – Posology and Method of Administration<br/>SmPC Section 4.4 – Special warnings and precautions for use<br/>SmPC Section 4.8 – Undesirable Effects</p> <p><b>Routine risk-minimization activities recommending specific clinical measures to address the risk:</b><br/>Section 4.2 (Dose modifications), Section 4.4 (QTc Prolongation) and Section 4.8 (undesirable effects) of the SmPC provide recommendations on risk management approach</p> <p><b>Other risk-minimization measures beyond the Product Information:</b><br/>None</p> <p><b>Medicine's legal status:</b><br/>Entrectinib is a prescription only medicine</p>                       |
| Neuro-developmental impairment in paediatric patients | <p><b>Routine risk communication:</b><br/>SmPC Section 4.2 – Posology and Method of Administration<br/>SmPC Section 4.4 – Special warnings and precautions for use<br/>SmPC Section 5.3 – Juvenile rat toxicology study</p> <p><b>Routine risk-minimization activities recommending specific clinical measures to address the risk:</b><br/>Section 4.2 (Dose modifications), Section 4.4 (Cognitive disorder) and Section 5.3 (Juvenile rat toxicology study) of the SmPC provide recommendations on risk management approach</p> <p><b>Other risk-minimization measures beyond the Product Information:</b><br/>None</p> <p><b>Medicine's legal status:</b><br/>Entrectinib is a prescription only medicine</p> |
| Severe neurologic reactions                           | <p><b>Routine risk communication:</b><br/>SmPC Section 4.2 – Posology and Method of Administration<br/>SmPC Section 4.4 – Special warnings and precautions for use<br/>SmPC Section 4.7 – Effects on ability to drive and use machines</p> <p><b>Routine risk-minimization activities recommending specific clinical measures to address the risk:</b><br/>Section 4.2 (Dose modifications), Section 4.4 (Cognitive disorder) and Section 4.7 (Effects on ability to drive and use machines) and of the SmPC provide recommendations on risk management approach</p>  |

| Safety concern                          | Routine risk-minimization activities   |
|---|--|
|   | <p><b>Other risk-minimization measures beyond the Product Information:</b><br/>None</p> <p><b>Medicine's legal status:</b><br/>Entrectinib is a prescription only medicine</p>   |
| Use in Patients with Hepatic Impairment | <p><b>Routine risk communication:</b><br/>SmPC Section 4.2 – Posology and Method of Administration (Special Populations)<br/>SmPC Section 5.2 – Pharmacokinetic Properties</p> <p><b>Routine risk-minimization activities recommending specific clinical measures to address the risk:</b><br/>Not applicable</p> <p><b>Other risk-minimization measures beyond the Product Information:</b><br/>None</p> <p><b>Medicine's legal status:</b><br/>Entrectinib is a prescription only medicine</p> |
| Safety in long term use                 | <p><b>Routine risk communication:</b><br/>SmPC Section 4.2 – Posology and Method of Administration (Special Populations)<br/>SmPC Section 5.2 – Pharmacokinetic Properties</p> <p><b>Routine risk-minimization activities recommending specific clinical measures to address the risk:</b><br/>Not applicable</p> <p><b>Other risk-minimization measures beyond the Product Information:</b><br/>None</p> <p><b>Medicine's legal status:</b><br/>Entrectinib is a prescription only medicine</p> |

SmPC=Summary of Product Characteristics.

## V.2. ADDITIONAL RISK-MINIMIZATION MEASURES

Routine risk-minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

### V.3 SUMMARY OF RISK-MINIMIZATION MEASURES

**Table 27 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern**

| Safety concern  | Risk minimization measures   | Pharmacovigilance activities  |
|---|--|---|
| Fractures   | <p><b>Routine risk-minimization measures:</b><br/>SmPC Section 4.4 (Fractures) and Section 4.8 (undesirable effects) of the SmPC provide recommendations on risk management approach</p> <p><b>Additional risk-minimization measures:</b><br/>None</p>                                       | <p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b><br/>None</p> <p><b>Additional pharmacovigilance activities:</b><br/>Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].</p> |
| Congestive Heart Failure                              | <p><b>Routine risk-minimization measures:</b><br/>SmPC Sections 4.2 (Dose modifications), Section 4.4 (Congestive heart failure) and Section 4.8 (undesirable effects) provide recommendations on risk management approach</p> <p><b>Additional risk-minimization measures:</b><br/>None</p> | <p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b><br/>None</p> <p><b>Additional pharmacovigilance activities:</b><br/>Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].</p> |
| QT Prolongation                                       | <p><b>Routine risk-minimization measures:</b><br/>SmPC Sections 4.2 (Dose modifications), Section, 4.4 (QTc prolongation) and Section 4.8 (undesirable effects) provide recommendations on risk management approach</p> <p><b>Additional risk-minimization measures:</b><br/>None</p>        | <p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b><br/>None</p> <p><b>Additional pharmacovigilance activities:</b><br/>Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG] and BO41932 [TAPISTRY].</p>  |
| Neuro-developmental Impairment in Paediatric Patients | <p><b>Routine risk-minimization measures:</b><br/>SmPC Sections 4.2 (Dose modifications), Section 4.4 (Cognitive disorders) and Section 5.3 – (Juvenile rat toxicology study provides available</p>  | <p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b><br/>None</p>  |

| Safety concern                          | Risk minimization measures  | Pharmacovigilance activities  |
|---|---|---|
|   | <p>information in animal studies) provide recommendations on risk management approach if neurocognitive changes development.</p> <p><b>Additional risk-minimization measures:</b><br/>None</p>  | <p><b>Additional pharmacovigilance activities:</b><br/>Risk continues to be further assessed as part of PAES CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].</p>  |
| Severe Neurologic Reactions             | <p><b>Routine risk-minimization measures:</b><br/>SmPC Sections 4.2 (Dose modifications), Section 4.4 (Cognitive disorders), Section 4.7 – Effects on ability to drive and use machines</p> <p><b>Additional risk-minimization measures:</b><br/>None</p> | <p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b><br/>None</p> <p><b>Additional pharmacovigilance activities:</b><br/>Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].</p> |
| Use in Patients with Hepatic Impairment | <p><b>Routine risk-minimization measures:</b><br/>None</p> <p><b>Additional risk-minimization measures:</b><br/>None</p>  | <p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b><br/>None</p> <p><b>Additional pharmacovigilance activities:</b><br/>Study GP41174</p>   |
| Safety in Long Term Use                 | <p><b>Routine risk-minimization measures:</b><br/>None</p> <p><b>Additional risk-minimization measures:</b><br/>None</p>  | <p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b><br/>None</p> <p><b>Additional pharmacovigilance activities:</b><br/>Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].</p> |

PAES=Post authorization efficacy study; SmPC=Summary of Product Characteristics.

## **REFERENCES**

- Aboukassim T, Tong XK, Tse YC, et al. Ligand-dependent TrkA activity in brain differentially affects spatial learning and long-term memory. *Mol Pharmacol*. 2011;80(3):498-508.
- Albain KS, Nag SM, Calderillo-Ruiz G, et al. Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol*. 2008;26:3950-3957.
- Ali A, Goffin JR, Arnold A, et al. Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. *Curr Oncol*. 2013;20:e300-306.
- Becker BK, Tian C, Zucker IH, Wang HJ. Influence of brain-derived neurotrophic factor-tyrosine receptor kinase B signalling in the nucleus tractus solitarius on baroreflex sensitivity in rats with chronic heart failure. *J Physiol*. 2016;594(19):5711-25.
- Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*. 2012;30:863-870.
- Besse B, Shaw AT, Solomon BJ, et al. Preliminary efficacy and safety of lorlatinib in patients (pts) with ROS1-positive non-small cell lung cancer (NSCLC). *Ann. Oncol*. 2017;28 (suppl. 5):v460-v496.
- Blanco JA, Toste IS, Alvarez RF, et al. Age, comorbidity, treatment decision, and prognosis in lung cancer. *Age Ageing*. 2008;37(6):715-718.
- Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627-1639.
- Bruno MA, Clarke PB, Seltzer A, Quirion R, Burgess K, Cuello AC, Saragovi HU. Long-lasting rescue of age-associated deficits in cognition and the CNS cholinergic phenotype by a partial agonist peptidomimetic ligand of TrkA. *J Neurosci*. 2004;24(37):8009-18.
- Bunn Jr. P. A. and Lilenbaum R. Chemotherapy for elderly patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst*. 2003;95 (5):341-343.
- Cameron D, Casey M, Oliva C, et al. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. *Oncologist*. 2010;15:924-934.
- Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat*. 2008;112:533-543.
- Cancer Research UK 2015, Cancer Research UK. Lung cancer risks and causes (<http://www.cancerresearchuk.org/about-cancer/type/lung-cancer/about/lung-cancer-risks-and-causes>).

- Capsoni S, Tiveron C, Vignone D, et al. Dissecting the involvement of tropomyosin-related kinase A and p75 neurotrophin receptor signaling in NGF deficit-induced neurodegeneration. *Proc Natl Acad Sci USA*. 2010 6;107(27):12299-304.
- Center for Drug Evaluation and Research (CDER). Assessment of abuse potential of drugs. January 2017.
- Chargari C, Kirov KM, Bollet MA at al. Cardiac toxicity in breast cancer patients: from a fractional point of view to a global assessment. *Cancer Treat Rev*. 2011;37(4):321-30.
- Chau NG, Hotte SJ, Chen EX, et al. A phase II study of sunitinib in recurrent and/or metastatic adenoid cystic carcinoma (ACC) of the salivary glands: current progress and challenges in evaluating molecularly targeted agents in ACC. *Ann Oncol*. 2012;23:1562-1570.
- Chi A, Komaki R. Treatment of brain metastasis from lung cancer. *Cancers (Basel)*. 2010;2:2100.
- Chmielecki J, Bailey M, He J, et al. Genomic Profiling of a Large Set of Diverse Pediatric Cancers Identifies Known and Novel Mutations across Tumor Spectra. *Cancer Res*. 2017;77:509-519.
- Clavé S, Gimeno J, Muñoz-Mármol AM, et al. ROS1 copy number alterations are frequent in non-small cell lung cancer. *Oncotarget*. 2016;16;7:8019-8028.
- Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet*. 2011;377:914-923.
- Cortot AB, Audigier-Valette C, Molinier O, et al. Weekly paclitaxel plus bevacizumab versus docetaxel as second or third-line treatment in advanced non-squamous non-small cell lung cancer (NSCLC): Results from the phase III study IFCT-1103 ULTIMATE. *J Clin Oncol*. 2016;34:(suppl; abstr 9005).
- Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol*. 2011;29:e443-445.
- Cowansage KK, LeDoux JE, Monfils MH. Brain-derived neurotrophic factor: a dynamic gatekeeper of neural plasticity. *Curr Mol Pharmacol*. 2010;3(1):12-29.
- Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol*. 2016;17:425-439.
- Davies KD, Le AT, Theodoro MF, et al. Identifying and targeting ROS1 gene fusions in non-small cell lung cancer. *Clin Cancer Res*. 2012;18:4570-4579.

- Dawe DE, Greenspoon JN, Ellis PM. Brain metastases in non-small-cell lung cancer. *Clin Lung Cancer*. 2014;15:249-257.
- Debeir T, Saragovi HU, Cuello AC. A nerve growth factor mimetic TrkA antagonist causes withdrawal of cortical cholinergic boutons in the adult rat. *Proc Natl Acad Sci USA*. 1999;96(7):4067-72.
- Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet*. 2006;368:1329-1338.
- Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: Results of a Phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016;34:786-793.
- Edwards BK, Noone AM, Mariotto AB et. al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer*. 2014;120(9):1290-314.
- Eichler AF, Loeffler JS. Multidisciplinary management of brain metastases. *Oncologist*. 2007;12:884-898.
- Entrectinib Summary of Product Characteristics (Version 1, 10/2018).
- European Cancer Observatory. Cancer Factsheets: Lung cancer including trachea and bronchus. [https://www.encl.eu/sites/default/files/factsheets/ENCR\\_Factsheet\\_Lung\\_2014.pdf](https://www.encl.eu/sites/default/files/factsheets/ENCR_Factsheet_Lung_2014.pdf)
- 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:E359-E386.
- Fokas E, Steinbach JP, Rödel C. Biology of brain metastases and novel targeted therapies: time to translate the research. *Biochim Biophys Acta*. 2013;1835:61-75.
- Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. *Oncologist*. 2013;18(7):865-75.
- Gainor JF, Tseng D, Yoda S, et al. Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non-small-cell lung cancer. *JCO Precis Oncol*. 2017.
- García-Del-Muro X, López-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol*. 2011;29:2528-2533.



- Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384:665-673.
- Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol*. 2007;25:1539-1544.
- Goldstein RE, Beiser GD, Stampfer M, Epstein SE. Impairment of autonomically mediated heart rate control in patients with cardiac dysfunction. *Circ Res*. 1975;36(5):571-8.
- Gridelli C, Perrone F, Monfardini S. Meeting highlights: Lung cancer in the elderly. *Eur J Cancer*. 1997;33(14):2313-2314.
- Grose D and Milroy R. Chronic obstructive pulmonary disease: a complex comorbidity of lung cancer. *Journal of Comorbidity*. 2011;1:45-50.
- Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:303-312.
- Halalsheh, H. et al. Dramatic bone remodeling following larotrectinib administration for bone metastasis in a patient with TRK fusion congenital mesoblastic nephroma. *Pediat. Blood Cancer* 65, e27271 (2018). Holcman, Martin et al. "Mouse Models of Receptor Tyrosine Kinases." Chapter 11 in: *Receptor Tyrosine Kinases: Structure, Functions and Role in Human Disease*. Ed. Deric L. Wheeler and Yosef Yarden. New York, NY: Springer New York, 2015. 279-438.
- Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol*. 2004;22:1589-1597.
- Havlik RJ, Yancik R, Long S, et al. The National Institute on Aging and the National Cancer Institute SEER Collaborative Study on Comorbidity and Early Diagnosis of Cancer in the Elderly. *Cancer* 1994;74:2101-6.
- Henley SJ, Richards TB, Underwood JM, et al.; Centers for Disease Control and Prevention (CDC). Lung cancer incidence trends among men and women--United States, 2005-2009. *MMWR Morb Mortal Wkly Rep*. 2014 Jan 10;63(1):1-5. Erratum in: *MMWR Morb Mortal Wkly Rep*. 2014;63(2):45. [<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6301a1.htm>].
- Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540-1550.

- Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, [https://seer.cancer.gov/csr/1975\\_2013/](https://seer.cancer.gov/csr/1975_2013/), based on November 2015 SEER data submission, posted to the SEER web site, April 2016.
- Inno A, Di Noia V, D'Argento E, et al. State of the art of chemotherapy for the treatment of central nervous system metastases from non-small cell lung cancer. *Transl Lung Cancer Res.* 2016;5:599-609.
- International Agency for Research on Cancer. Lung Cancer. 2018. <http://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf>
- Isbister GK, Page CB. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. *Br J Clin Pharmacol.* 2013;76(1):48-57
- Jakob JA, Kies MS, Glisson BS, et al. Phase II study of gefitinib in patients with advanced salivary gland cancers. *Head Neck.* 2015;37:644-649.
- Janssen-Heijnen ML, Houterman S, Lemmens VE, et al. Prognostic impact of increasing age and comorbidity in cancer patients: a population-based approach. *Crit Rev Oncol Hemat.* 2005;55:231-240.
- Katayama R, Sakashita T, Yanagitani N, et al. P-glycoprotein mediates ceritinib resistance in anaplastic lymphoma kinase-rearranged non-small cell lung cancer. *EBioMedicine.* 2015;3:54-66.
- Krenz NR, Meakin SO, Krassioukov AV, Weaver LC. Neutralizing intraspinal nerve growth factor blocks autonomic dysreflexia caused by spinal cord injury. *J Neurosci.* 1999 Sep 1;19(17):7405-14.
- Laurie SA, Siu LL, Winkquist E, et al. A phase 2 study of platinum and gemcitabine in patients with advanced salivary gland cancer: a trial of the NCIC Clinical Trials Group. *Cancer.* 2010;116:362-368.
- Lu Y, Christian K, Lu B. BDNF: a key regulator for protein synthesis-dependent LTP and long-term memory? *Neurobiol Learn Mem.* 2008;89(3):312-23.
- Marsh DR, Wong ST, Meakin SO, et al. Neutralizing intraspinal nerve growth factor with a trkA-IgG fusion protein blocks the development of autonomic dysreflexia in a clip-compression model of spinal cord injury. *J Neurotrauma.* 2002 Dec;19(12):1531-41.
- Mathieu D, Kondziolka D, Cooper PB, et al. Gamma knife radiosurgery for malignant melanoma brain metastases. *Clin Neurosurg.* 2007;54:241-247.
- Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med.* 2015;372:1909-1919.
- McMurray JJ, Pfeffer MA. Heart Failure. *Lancet.* 2005;365(9474):1877-89.

- Metro G, Chiari R, Ricciuti B, et al. Pharmacotherapeutic options for treating brain metastases in non-small cell lung cancer. *Expert Opin Pharmacother*. 2015;16:2601-2613.
- Meyers CA. Neurocognitive dysfunction in cancer patients. *Oncology (Williston Park)*. 2000;14(1):75-9; discussion 79, 81-2, 85.
- Miller WL. Fluid Volume Overload and Congestion in Heart Failure: Time to Reconsider Pathophysiology and How Volume Is Assessed. *Circ Heart Fail*. 2016;9(8):e002922.
- Mir O, Brodowicz T, Italiano A, et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2016;17:1732-1742.
- Molina JR, Yang P, Cassivi SD, et al. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc*. 2008;83:584-594.
- Monteggia LM, Barrot M, Powell CM, et al. Essential role of brain-derived neurotrophic factor in adult hippocampal function. *Proc Natl Acad Sci U S A*. 2004;101(29):10827-32.
- Moore HC. An overview of chemotherapy-related cognitive dysfunction, or 'chemobrain'. *Oncology (Williston Park)*. 2014;28(9):797-804.
- National Cancer Institute; Non-Small Cell Lung Cancer Treatment (PDQ)- Health Professional Version. [<http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional>].
- National Clinical Guideline Centre (UK). Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management. 2018. [<https://www.ncbi.nlm.nih.gov/pubmed/22741186>]
- Nieder C, Mehta MP, Geinitz H, et al. Prognostic and predictive factors in patients with brain metastases from solid tumors: A review of published nomograms. *Crit Rev Oncol Hematol*. 2018;126:13-18.
- Novello S, Barlesi F, Califano R, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27(suppl 5):v1-v27.
- O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol*. 2002;20:2812-2823.
- Ou SH, Jänne PA, Bartlett CH, et al. Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. *Ann Oncol*. 2014;25:415-422.
- Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. *Drug Saf*. 2000;22(4):263-302.

- Partida E, Mironets E, Hou S, Tom VJ. Cardiovascular dysfunction following spinal cord injury. *Neural Regen Res*. 2016;11(2):189-94.
- Patil T, Smith DE, Bunn PA, et al. The incidence of brain metastases in stage IV ROS1-rearranged non-small cell lung cancer and following progression on crizotinib. *J Thorac Oncol*. 2018;13(11):1717-1726.
- Patterson SL, Abel T, Deuel TA, et al. Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. *Neuron*. 1996;16(6):1137-45.
- Pavlick D, Schrock AB, Malicki D, et al. Identification of NTRK fusions in pediatric mesenchymal tumors. *Pediatr Blood Cancer*. 2017;64.
- Peeters M, Price TJ, Cervantes A, et al. Randomized Phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol*. 2010;28:4706-4713.
- Perrin JM, Bloom SR, Gortmaker SL. The increase of childhood chronic conditions in the United States. *JAMA*. 2007;297(24):2755-9.
- Peters S, Camidge DR, Shaw AT, et al. Entrectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377:829-838.
- Piccirillo JF, Vlahiotis A, Barrett LB, et al. The changing prevalence of comorbidity across the age spectrum. *Crit Rev Oncol Hematol*. 2008 Aug;67(2):124-32.
- Population PK and PK/PD Data Analysis Report. Data analysis report of the population pharmacokinetics, exposure-efficacy and exposure-safety relationships in patients with advanced/metastatic solid tumors treated with entrectinib. Report 1091319. November 2018.
- Raizman MB, Hamrah P, Holland EJ, et al. Drug-induced corneal epithelial changes. *Surv Ophthalmol*. 2017;62(3):286-301.
- Reck M, Kaiser R, Mellempgaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol*. 2014a;15:143-155.
- Reck M, Popat S, Reinmuth N, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014b;25 Suppl 3:iii27-39.
- Redmond AJ, Diluna ML, Hebert R, et al. Gamma knife surgery for the treatment of melanoma metastases: the effect of intratumoral hemorrhage on survival. *J Neurosurg*. 2008;109(Suppl):99–105.
- Ries LAG, Eisner MP, Kosary CL, et al: SEER Cancer Statistics Review 1975–2000. [http://seer.cancer.gov/csr/1975\\_2000](http://seer.cancer.gov/csr/1975_2000).

- Rimkunas VM, Crosby KE, Li D, et al. Analysis of receptor tyrosine kinase ROS1-positive tumors in non-small cell lung cancer: identification of a FIG-ROS1 fusion. *Clin Cancer Res.* 2012;18:4449-4457.
- Scheffler M, Schultheis A, Teixeira C, et al. ROS1 rearrangements in lung adenocarcinoma: prognostic impact, therapeutic options and genetic variability. *Oncotarget.* 2015;6:10577-85.
- Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2016;387:1629-1637.
- Selroos O, Kupczyk M, Kuna P, et al. National and regional asthma programmes in Europe. *Eur Respir Rev.* 2015;24(137):474-83.
- Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT interval). *Drug Saf.* 2013;36(5):295-316.
- Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med.* 2014;371:1963-1671.
- Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol.* 2000;18:2095-2103.
- Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin.* 2012;62:10-29.
- Silvestri GA, Gould MK, Margolis ML, et al. Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest.* 2007;132(3 Suppl):178S-201S.
- Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol.* 2008;26:2311-2319.
- Spector LG, Pankratz N, Marcotte EL. Genetic and nongenetic risk factors for childhood cancer. *Pediatr Clin North Am.* 2015 Feb;62(1):11-25.
- Stransky N, Cerami E, Schalm S, et al. The landscape of kinase fusions in cancer. *Nat Commun.* 2014;5:4846.
- Strevel EL, Ing DJ, Siu LL. Molecularly targeted oncology therapeutics and prolongation of the QT interval. *J Clin Oncol.* 2007;25(22):3362-71.
- Su, YW et al. Roles of neurotrophins in skeletal tissue formation and healing. *J Cell Physiol.* 2018 Mar;233(3):2133-2145.

- Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol.* 2015;16:499-508.
- Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. *Nat Med.* 2012;18:378-381.
- Tang SC, Nguyen LN, Sparidans RW, et al. Increased oral availability and brain accumulation of the ALK inhibitor crizotinib by coadministration of the P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) inhibitor elacridar. *Int J Cancer.* 2014;134:1484-1494.
- Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. *Lancet.* 2016;388:488-497.
- Tiersten A, Wo J, Jacobson C, et al. Cardiac toxicity observed in association with high-dose cyclophosphamide-based chemotherapy for metastatic breast cancer. *Breast.* 2004 Aug;13(4):341-6.
- Tomlinson, Ryan E., et al. "NGF-TrkA signaling in sensory nerves is required for skeletal adaptation to mechanical loads in mice." *Proceedings of the National Academy of Sciences* 114.18 (2017): E3632.
- Vallebona A. Cardiac damage following therapeutic chest irradiation. Importance, evaluation and treatment. *Minerva Cardioangiol.* 2000 Mar;48(3):79-87.
- Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol.* 2012;30:3499-3506.
- van de Schans SAM, Janssen-Heijnen MLG, Biesma B, et al. COPD in cancer patients: higher prevalence in the elderly, a different treatment strategy in case of primary tumors above the diaphragm, and a worse overall survival in the elderly patient. *Eur J Cancer.* 2007;43:2194-20.
- van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2012;379:1879-1886.
- Van Kruijsdijk RC, van der Graaf Y, Peeters PH, et al. Cancer risk in patients with manifest vascular disease: effects of smoking, obesity, and metabolic syndrome. *Cancer Epidemiol Biomarkers Prev.* 2013;22(7):1267-77.
- Wang S, Wong ML, Hamilton N, et al. Impact of age and comorbidity on non-small cell lung cancer treatment in older veterans. *J Clin Oncol.* 2012;30(13):1447-1455.
- Wingo PA, Cardinez CJ, Landis SH, et al: Long term trends in cancer mortality in the United States. *Cancer* 97:3133-3275, 2003 (suppl 12).

World Health Organisation. Global status report on noncommunicable diseases 2010: Description of the global burden of NCDs, their risk factors and determinants. 2011.

World Health Organisation. Situation of child and adolescent health in Europe. 2017.

Wu YL, Yang JC, Kim DW, et al. Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2018;36:1405-1411.

Xalkori EU Assessment Report; EMA/CHMP/327604/2016.

Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013 Oct 15;128(16):1810-52.

Zehir A, Benayed R1, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nat Med*. 2017;23(6):703-713.

Zucker IH, Patel KP & Schultz HD. Neurohumoral stimulation. *Heart Fail Clin*. 2012;8(1):87-99.

Zucker IH, Schultz HD, Patel KP, et al. Regulation of central angiotensin type 1 receptors and sympathetic outflow in heart failure. *Am J Physiol Heart Circ Physiol*. 2009;297(5):H1557-66.

## **PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN**

### **SUMMARY OF RISK MANAGEMENT PLAN FOR ROZLYTREK<sup>®</sup> (ENTRECTINIB)**

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

Rozlytrek SmPC and its package leaflet give essential information to healthcare professionals and patients on how Rozlytrek should be used.

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

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

#### **I. THE MEDICINE AND WHAT IT IS USED FOR**

Rozlytrek is authorized for the treatment of NTRK fusion-positive locally advanced or metastatic solid tumors and ROS1-positive, advanced non-small cell lung cancer (NSCLC) (see SmPC for the full indication). It contains entrectinib as the active substance, and it is given by oral administration.

Further information about the evaluation of Rozlytrek benefits can be found in Rozlytrek EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page.

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

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

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

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



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

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

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

If important information that may affect the safe use of Rozlytrek is not yet available, it is listed under “missing Information” below.

## II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Rozlytrek are risks that need special risk management activities to further investigate or minimize 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 Rozlytrek. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information about the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long term use of the medicine).

| List of Important Risks and Missing Information |  |
|---|--|
| Important identified risks                      | <ul style="list-style-type: none"> <li>• Congestive Heart Failure</li> <li>• QT Prolongation</li> <li>• Fractures</li> </ul>                     |
| Important potential risks                       | <ul style="list-style-type: none"> <li>• Severe neurologic reactions</li> <li>• Neuro-developmental impairment in paediatric patients</li> </ul> |
| Missing information                             | <ul style="list-style-type: none"> <li>• Use in Patients with Hepatic Impairment</li> <li>• Safety in long term use</li> </ul>                   |

## II.B SUMMARY OF IMPORTANT RISKS

| <b>Important Identified Risk: Fractures</b>   |   |
|---|---|
| Evidence for linking the risk to the medicine | Evidence is based on the safety data from two Phase I/Ib studies (GO40783 [ALKA], GO40784 [STARTRK-1]) one Phase I/II CO40778 [STARTRK-NG] and one Phase II study (GO40782 [STARTRK-2]) of entrectinib, in adults, adolescents, and children (504 patients) with, ROS1, NTRK1/2/3 or ALK alterations or fusions who received at least one dose of entrectinib |
| Risk factors and risk groups                  | In adult patients, the most common cause of fractures appears to be by accidental injury. It is known that entrectinib may cause dizziness and ataxia in patients, though this seemed to be a factor in few of the falls leading to the fractures.  |
| Risk-minimization measures                    | <p><b>Routine risk-minimization measures:</b><br/>SmPC Section 4.4 (Fractures) and Section 4.8 of the SmPC provide recommendations on risk management approach</p> <p><b>Additional risk-minimization measures:</b><br/>None</p>  |
| Additional pharmacovigilance activities       | Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].   |

SmPC=Summary of Product Characteristics.

| <b>Important Identified Risk: Congestive Heart Failure</b> |   |
|--|---|
| Evidence for linking the risk to the medicine              | Evidence is based on the safety data from two Phase I/Ib studies (GO40783 [ALKA], GO40784 [STARTRK-1]) one Phase I/II (CO40778 [STARTRK-NG]) and one Phase II study (GO40782 [STARTRK-2]) of entrectinib, in adults, adolescents, and children (504 patients) with, ROS1, NTRK1/2/3 or ALK alterations or fusions who received at least one dose of entrectinib   |
| Risk factors and risk groups                               | Risk factors of heart failure include a medical history of coronary artery disease including a previous myocardial infarction, age >65 years, smoking, body mass index > 27 kg/m <sup>2</sup> , sedentary life style, abnormality in lipidi profile, hypertension, diabetes, atrial fibrillation, valvular heart disease, alcohol abuse, infection, and cardiomyopathy of an unknown cause<br><br>In addition, prior cancer treatments including the most commonly used chemotherapy agents (e.g., anthacyclines, cyclophosphamide and radiation therapy) and biologic and targeted therapy drugs, can induce cardiac disorders |
| Risk-minimization measures                                 | <b>Routine risk-minimization measures:</b><br>SmPC Sections 4.2 (Dose modifications) and 4.4 (Congestive heart failure) and Section 4.8 (undesirable effects) provide recommendations on risk management approach<br><b>Additional risk-minimization measures:</b><br>None  |
| Additional pharmacovigilance activities                    | Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY]  |

SmPC=Summary of Product Characteristics.

| <b>Important Identified Risk: QT Prolongation</b> |   |
|---|---|
| Evidence for linking the risk to the medicine     | Evidence is based on the safety data from two Phase I/Ib studies (GO40783 [ALKA], GO40784 [STARTRK-1]), one Phase I/II study (CO40778 [STARTRK-NG]) and one Phase II study (GO40782 [STARTRK-2]) of entrectinib, in adults, adolescents, and children (504 patients) with, ROS1, NTRK1/2/3 or ALK alterations or fusions who received at least one dose of entrectinib  |
| Risk factors and risk groups                      | <p>QTc prolongation appears to occur more frequently in females. Inherited genetic polymorphisms or mutations with low penetrance, involving the same gene loci associated with phenotypically expressed long-QT syndrome, may underlie individual idiosyncrasies to the acquired form in many, if not most, cases. Some individuals have QT prolongation throughout life without any manifest arrhythmias, while others are highly susceptible to symptomatic arrhythmias, particularly torsades de pointes.</p> <p>Risk factors for QTc prolongation may also include patients with pre-existing conditions such as history of cardiac dysrhythmia, electrolyte disturbances, cardiac ischemia, and the concomitant use of medications with the potential to prolong QTc.</p> |
| Risk-minimization measures                        | <p><b>Routine risk-minimization measures:</b><br/>SmPC Sections 4.2 (Dose modifications) and 4.4 (QTc prolongation) and Section 4.8 (undesirable effects) provide recommendations on risk management approach</p> <p><b>Additional risk-minimization measures:</b><br/>None</p>   |
| Additional pharmacovigilance activities           | Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY]  |

SmPC=Summary of Product Characteristics.

| <b>Important Potential Risk: Severe Neurological Reactions</b> |   |
|--|---|
| Evidence for linking the risk to the medicine                  | Evidence is based on the safety data from two Phase I/Ib studies (GO40783 [ALKA], GO40784 [STARTRK-1]), one Phase I/II study (CO40778 [STARTRK-NG]) and one Phase II study (GO40782 [STARTRK-2]) of entrectinib, in adults, adolescents, and children (504 patients) with, ROS1, NTRK1/2/3 or ALK alterations or fusions who received at least one dose of entrectinib  |
| Risk factors and risk groups                                   | Patients with metastatic brain tumours can develop substantial cognitive disability, but the extent and type of cognitive dysfunction often varies from patient to patient because of differential tumour volume and location. In the entrectinib clinical trial program, 96.3% of patients had metastatic disease and 22.2% had CNS metastases at baseline per investigator assessment. Chemotherapy-induced cognitive dysfunction is a common side effect and cause of morbidity in cancer patients and the majority (85.2%) of patients receiving entrectinib were previously treated with chemotherapy. Memory, attention, psychomotor function, processing speed, and executive function appear to be commonly affected. |
| Risk-minimization measures                                     | <p><b>Routine risk-minimization measures:</b><br/>SmPC Sections 4.2 (Dose modifications), 4.4 (Cognitive disorders) and 4.7 (Effects on ability to drive and use machines), provide recommendations on risk management approach</p> <p><b>Additional risk-minimization measures:</b><br/>None</p>   |
| Additional pharmacovigilance activities                        | Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].   |
| SmPC=Summary of Product Characteristics.                       |   |

| <b>Important Potential Risk: Neuro-developmental impairment in paediatric patients</b> |  |
|--|--|
| Evidence for linking the risk to the medicine  | Evidence is based on a 13-week juvenile rat toxicology study animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood in humans). In addition to CNS and skin effects, and decreased RBC parameters, effects on growth and development were observed in the dosing and recovery phases including decreased body weight gain and delayed sexual maturation (at $\geq 4$ mg/kg/day, approximately 0.1 times the human exposure by AUC at the recommended dose), deficits in neurobehavioral assessments including functional observational battery and learning and memory (at $\geq 8$ mg/kg/day, approximately 0.2 times the human exposure by AUC at the recommended dose). |
| Risk factors and risk groups   | Young children treated with entrectinib for an extended duration up to adult maturity.   |
| Risk-minimization measures   | <b>Routine risk-minimization measures:</b><br>Section 4.2 (Dose modifications), Section 4.4 (Cognitive disorder) and Section 5.3 (Juvenile rat toxicology study) of the SmPC provide recommendations on risk management approach.<br><b>Additional risk-minimization measures:</b><br>None   |
| Additional pharmacovigilance activities  | Risk continues to be further assessed as part of PAES CO40778 [STARTRK-NG], and BO41932 [TAPISTRY]   |
| SmPC=Summary of Product Characteristics.   |  |

| <b>Missing Information: Use in Patients with Hepatic Impairment</b> |   |
|---|---|
| Risk-minimization measures  | <b>Routine risk-minimization measures:</b><br>None<br><b>Additional risk-minimization measures:</b><br>None |
| Additional pharmacovigilance activities                             | Study GP41174   |

| <b>Missing Information: Safety in long term use</b> |   |
|---|---|
| Risk factors and risk groups                        | Patients treated with entrectinib for greater than 12 months.   |
| Risk-minimization measures                          | <b>Routine risk-minimization measures:</b><br>None<br><b>Additional risk-minimization measures:</b><br>None           |
| Additional pharmacovigilance activities             | Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], BO41932 [TAPISTRY]. |

## II.C POST-AUTHORIZATION DEVELOPMENT PLAN

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

| <b>Study Status</b>   | <b>Rationale and objectives</b>  | <b>Deadline</b>  |
|---|--|------------------|
| [ANX] MO41552<br>Randomized, open-label, multicenter, Phase 3 study of entrectinib versus crizotinib in patients who have non-small cell lung cancer (NSCLC) harbouring ROS1 gene rearrangements with and without central nervous system metastases.<br>Ongoing | In order to further characterise the efficacy of entrectinib in patients with baseline CNS disease, the MAH should conduct and submit the results of a randomised controlled trial versus crizotinib in treatment naïve ROS1 NSCLC patients. The primary endpoint will be PFS in the subgroup of patients with CNS metastases at baseline. | 31 December 2027 |



| Studies contributing to pooled analysis<br>Status   | Rationale and objectives  | Deadline             |
|---|---|----------------------|
| <p>[SOB] GO40782 (STARTRK-2)<br/>An open-label, multicenter, global Phase 2 basket study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumours that harbor NTRK1/2/3, ROS1, or ALK gene rearrangements.<br/>Ongoing</p> <p>[SOB] CO40778 (STARTRK-NG)<br/>A phase 1/2, open-label, dose-escalation and expansion study of entrectinib (RXDX-101) in pediatrics with locally advanced or metastatic solid or primary CNS tumors and/or who have no satisfactory treatment options.<br/>Ongoing</p> <p>[SOB] BO41932 (TAPISTRY)<br/>A Phase 2, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in patients with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations or who are TMB-high as identified by a validated NGS assay. Objective of cohort B is to evaluate the efficacy of entrectinib in patients with NTRK1/2/3 fusion-positive advanced or metastatic solid tumours.<br/><br/>Ongoing</p> | <p>In order to further confirm the histology-independent efficacy of entrectinib in adult and paediatric patients, the MAH should submit a pooled analysis for an increased sample size of NTRK fusion-positive patients from the ongoing studies STARTRK-2, STARTRK-NG and any additional clinical trial conducted according to an agreed protocol.</p> <p>The MAH should submit the results of an interim safety and efficacy analysis of the NTRK efficacy-evaluable adult and paediatric patients including adolescents that are available as per integrated statistical analysis plan.</p> | <p>31 March 2027</p> |

ALK=Anaplastic lymphoma kinase; NTRK=neurotrophic receptor tyrosine kinase.

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

| <b>Study Status</b>  | <b>Rationale and objectives</b>  | <b>Deadline</b>   |
|--|--|---|
| [MEA] GP41174<br>Pharmacokinetic trial to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics and safety of Rozlytrek (entrectinib) compared to subjects with normal hepatic function<br><br>Ongoing | Missing information topic 'use in patients with hepatic impairment:<br>To determine the safety of entrectinib in patients with moderate and severe hepatic impairment, and also the impact of hepatic impairment on the pharmacokinetics of entrectinib in patients with moderate and severe hepatic impairment                | 31 December 2022  |
| Integrated safety analysis report to assess risk of fracture based on GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY] studies (PAESs)<br><br>Ongoing   | Report to characterize the risk of fractures in paediatric patients where the following bone biomarkers will be assessed: Serial assessments of BMD with DXA; bone biomarkers in blood and assessment of potential impairment of bone growth with serial hand/wrist and knee X-rays<br><br>Clinical summary of fracture events | Final integrated analysis report for bone biomarkers:<br>31 March 2025<br><br>Interim report will include clinical summary of fracture events:<br>With annual re-assessment |
|  | Report to characterize the risk of fractures in adult patients where the following bone biomarkers will be assessed: Serial assessments of bone mineral density (BMD) with dual X-ray absorptiometry (DXA) and bone biomarkers in blood<br><br>Clinical summary of fracture events   | Final integrated analysis report for bone biomarkers:<br>31 March 2025<br><br>Interim report will include clinical summary of fracture events:<br>With annual re-assessment |
|  | Report on congestive heart failure: incidence, severity, clinical outcome and reversibility will be characterized  | Final integrated analysis report for cardiac risks:<br>30 June 2022<br><br>Interim report:<br>With annual re-assessment   |
|  |  |   |

**ANNEX 1**  
**EUDRAVIGILANCE INTERFACE**

**ANNEX 1**  
**EUDRAVIGILANCE INTERFACE**

Available in electronic format only

## **ANNEX 2**

### **TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAM**

## ANNEX 2

### TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAM

**Table 1 Planned and Ongoing Studies**

| <b>Study Status</b>   | <b>Summary of Objectives</b>   | <b>Safety Concerns Addressed</b>  | <b>Protocol Link Milestones</b>   |
|---|--|---|---|
| Study GP41174 ongoing   | Pharmacokinetic trial to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics and safety of Rozlytrek (entrectinib) compared to subjects with normal hepatic function   | Missing information topic 'use in patients with hepatic impairment: To determine the safety of entrectinib in patients with moderate and severe hepatic impairment, and also the impact of hepatic impairment on the pharmacokinetics of entrectinib in patients with moderate and severe hepatic impairment. | Final clinical study report<br>31 December 2022   |
| Integrated safety analysis report to assess risk of fracture based on GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY] studies (PAESs) | Report to characterize the risk of fractures in paediatric patients where the following bone biomarkers will be assessed: Serial assessments of BMD with DXA; bone biomarkers in blood and assessment of potential impairment of bone growth with serial hand/wrist and knee X-rays.<br>Clinical summary of fracture events. | Risk of fractures   | Final integrated analysis report for bone biomarkers:<br>31 March 2025                        |
|   |  |   | Interim report will include clinical summary of fracture events:<br>With annual re-assessment |
|   | Report to characterize the risk of fractures in adult patients where the following bone biomarkers will be assessed: Serial assessments of bone mineral density (BMD) with dual X-ray absorptiometry (DXA) and bone  | Risk of fractures   | Final integrated analysis report for bone biomarkers:<br>31 March 2025                        |
|   |  |   | Interim report will include   |

| <b>Study Status</b>  | <b>Summary of Objectives</b>   | <b>Safety Concerns Addressed</b> | <b>Protocol Link Milestones</b>                                     |
|--|--|----------------------------------|---|
|  | biomarkers in blood.<br>Clinical summary of fracture events.   |                                  | clinical summary of fracture events:<br>With annual re-assessment   |
| Integrated safety analysis report to assess cardiac risks based on GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY] studies (PAESs) | Report on congestive heart failure: incidence, severity, clinical outcome and reversibility will be characterized. | Risk of congestive heart failure | Final integrated analysis report for cardiac risks:<br>30 June 2022 |
|  |  |                                  | Interim report:<br>With annual re-assessment                        |

**Table 2 Completed studies**

| <b>Study Status</b> | <b>Summary of Objectives</b> | <b>Safety Concerns Addressed</b> | <b>Date of Final Study Report Submission<br/>Link to report</b> |
|---------------------|------------------------------|----------------------------------|---|
| Not applicable      |                              |                                  |   |



## **ANNEX 3**

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

## **ANNEX 3**

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

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

| Study          | Protocol Title | Protocol Version | Protocol Date |
|----------------|----------------|------------------|---------------|
| Not Applicable |                |                  |               |

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

| Study          | Protocol Title | Protocol Number /Version | Protocol Date |
|----------------|----------------|--------------------------|---------------|
| Not Applicable |                |                          |               |

3. **PART C: PREVIOUSLY AGREED PROTOCOLS FOR ONGOING STUDIES AND FINAL PROTOCOLS NOT REVIEWED BY THE COMPETENT AUTHORITY**

**Approved Protocols**

| Study          | Protocol Title | Protocol Number/Version | Protocol Date | Procedure Number |
|----------------|----------------|-------------------------|---------------|------------------|
| Not Applicable |                |                         |               |                  |

**Final Protocols Not Reviewed or Not Approved**

| Study   | Protocol Title   | Protocol Number/Version | Protocol Date   |
|---------|--|-------------------------|-----------------|
| GP41174 | An open-label, one treatment, four group, parallel group study to investigate the effect of impaired hepatic function on the pharmacokinetics of entrectinib in volunteers with different levels of hepatic function | 2                       | 3 February 2020 |

| Study   | Protocol Title  | Protocol Number/<br>Version | Protocol Date     |
|---|---|-----------------------------|-------------------|
| <b>RXDX-101-02<br/>STARTRK-2<br/>GO40782</b>  | An open-label, multicenter, global phase 2 basket study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumours that harbor NTRK1/2/3, ROS1, or ALK gene rearrangements.                     | 9                           | 5 August 2021     |
| <b>RXDX-101-03<br/>STARTRK-NG<br/>CO40778</b> | A phase 1/2, open-label, dose-escalation and expansion study of entrectinib (RXDX-101) in pediatrics with locally advanced or metastatic solid or primary CNS tumors and/or who have no satisfactory treatment options.             | 10                          | 22 September 2021 |
| <b>TAPISTRY<br/>BO41932</b>                   | Tumor-agnostic precision immunoncology and somatic targeting rational for you (TAPISTRY) phase II platform trial  | 2                           | 14 May 2021       |
| <b>MO41552</b>                                | Randomized, open label, multicenter, phase 3 study of entrectinib versus crizotinib in patients who have non-small cell lung cancer (NSCLC) harbouring ROS1 gene rearrangements with and without central nervous system metastases. | 3                           | 18 May 2021       |

**ANNEX 4**

**SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS**

**ANNEX 4**  
**SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS**

Not applicable

**ANNEX 5**

**PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP**  
**PART IV**

## ANNEX 5

### PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

| Study   | Protocol Title  | Protocol Version | Protocol Date     |
|---|---|------------------|-------------------|
| <b>RXDX-101-03<br/>(STARTRK-NG)<br/>CO40778</b> | A phase I/II, open-label, dose-escalation and expansion study of entrectinib (RXDX-101) in pediatrics with locally advanced or metastatic solid or primary CNS tumors and/or who have no satisfactory treatment options             | 10               | 22 September 2021 |
| <b>RXDX-101-02<br/>(STARTRK-2)<br/>GO40782</b>  | An open-label, multicenter, global phase 2 basket study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbor NTRK1/2/3, ROS1, or ALK gene rearrangements                       | 9                | 5 August 2021     |
| <b>MO41552</b>                                  | Randomized, open label, multicenter, phase 3 study of entrectinib versus crizotinib in patients who have non-small cell lung cancer (NSCLC) harbouring ROS1 gene rearrangements with and without central nervous system metastases. | 3                | 18 May 2021       |
| <b>TAPISTRY<br/>BO41932</b>                     | Tumor-agnostic precision immuno-oncology and somatic targeting rational for you (TAPISTRY) phase II platform trial  | 2                | 14 May 2021       |



## **ANNEX 6**

### **DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)**

## **ANNEX 6**

### **DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)**

Not applicable

**ANNEX 7**

**OTHER SUPPORTING DATA**

**(INCLUDING REFERENCED MATERIAL)**

## **ANNEX 7**

### **OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)**

Not applicable

**ANNEX 8**

**SUMMARY OF CHANGES TO THE RISK-MANAGEMENT PLAN  
OVER TIME**

## ANNEX 8

### SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

| Version            | Approval date <sup>a</sup><br>Procedure | Change(s)  |
|--------------------|---|--|
| 1.1                | Not applicable                          | <ul style="list-style-type: none"> <li>Addressing the Day 120 CHMP List of Questions (LoQ for MAA procedure EMEA/H/C/004936)</li> </ul>  |
| 1.2                | Not applicable                          | <ul style="list-style-type: none"> <li>Addressing the Day 180 CHMP List of Outstanding Issues (1<sup>st</sup> LoOI for MAA procedure EMEA/H/C/4936).</li> </ul>  |
| 1.3                | Not applicable                          | <ul style="list-style-type: none"> <li>Addressing the Day 180 CHMP 2<sup>nd</sup> List of Outstanding Issues (2<sup>nd</sup> LoOI for MAA procedure EMEA/H/C/4936).</li> </ul>   |
| 1.4 (not released) | Not applicable                          | <ul style="list-style-type: none"> <li>Addressing the requests from the Assessors' report of the Applicant's responses to the Day 180 CHMP 2<sup>nd</sup> List of Outstanding Issues</li> </ul>  |
| 2                  | 28 May 2020<br>EMEA/H/C/004936          | <ul style="list-style-type: none"> <li>Addressing Assessor's comments received on 26, 27, 28 and 29 May 2020.</li> <li>This Entrectinib EU RMP version 2 is the first EU RMP approved by the CHMP and addresses all the review comments raised Assessors cumulatively during the initial Marketing Authorisation Application.</li> </ul> |
| 3                  | Not Applicable                          | <ul style="list-style-type: none"> <li>Inclusion of the TAPISTRY (BO41932) study as a post-approval efficacy study.</li> </ul>   |
| 3.1                |   | <ul style="list-style-type: none"> <li>A post authorization measure (PAM) has been submitted to the European Medicines Agency (EMA) for approval of Study BO41932 (TAPISTRY) as an additional trial to fulfil the Rozlytrek specific obligation (SOB). This EU RMP is updated to version 3.1 post approval of PAM.</li> </ul>            |

<sup>a</sup> Refers to the date of CHMP positive opinion. Note, not all versions of the EU RMP are approved by the CHMP.