EU RISK MANAGEMENT PLAN FOR ROZLYTREK®/ENTRECTINIB

RMP version to be assessed as part of this application:

RMP Version number: 6.1

Data lock point for this RMP: 4 December 2024

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
31-Mar-2025 07:27:36	Deputy QPPV	[redacted]
31-Mar-2025 23:56:49	Company Signatory (PV)	[redacted]

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Rationale for Submitting an Updated RMP

The entrectinib (Rozlytrek®) European Union (E.U.) Risk Management Plan (RMP) Version 6.1 was prepared to address PRAC feedback from the Assessment Report for procedure EMEA/H/C/004936/II/0025. Pregnancy follow-up questionnaires and the information presented for the summary table of additional pharmacovigilance activities has been removed.

Summary of Significant Changes in This RMP

- **Part III, Module III.1 Other forms of routine pharmacovigilance activities for pregnancy and/or breastfeeding**: Roche standard wording for pregnancy follow-up process was removed.
- **Part III, Module III.3 Summary table of additional pharmacovigilance activities**: Information referring to PAES was removed as this is presented in subsequent Part IV
- Annex 8: A summary of changes was provided for EU RMP v6.1.

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: 5.2

Approved with Procedure Number: EMEA/H/C/004936/X/0017/G

Date of approval (opinion date): 25 April 2024

See page 1 for signature and date

[redacted] (Deputy E.U. QPPV) | Date

See page 1 for signature and date

[redacted] (Clinical Safety Approver) | Date

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance(s) (INN or common name)	Entrectinib
Pharmacotherapeutic group(s) (ATC Code)	L01XE14
Marketing Authorisation Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	Rozlytrek®
Marketing authorisation procedure	Centralized
Brief description of the product	**Chemical class:** Antineoplastic agent, Tyrosine Kinase inhibitor
	Summary of mode of action: 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.
	Important information about its composition: • Each 100 mg hard capsule contains 65 mg lactose. Each 200 mg hard capsule contains 130 mg lactose. • 200 mg hard capsules contain 0.6 mg of the azo colouring agent sunset yellow FCF (E 110, FD&C yellow #6).
Hyperlink to the Product Information	Refer to Product Information

<table>
<tr><td rowspan="2">Indication(s) in the EEA</td><td>Current:
Neurotrophic tyrosine receptor kinase (NTRK) gene fusion
Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients older than 1 month with solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,
• who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
• who have not received a prior NTRK inhibitor
• who have no satisfactory treatment options.

ROS1 gene fusion
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.</td></tr>
<tr><td>Proposed:
Not applicable.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:
Adults
The recommended dose for adults is 600 mg entrectinib once daily.
Paediatric population
Paediatric population ＞6 months of age
The recommended dose for paediatric patients ＞6 months of age is based on body surface area (BSA) (see table). Patients who have difficulty or are unable to swallow capsules but can swallow soft food, may receive treatment with Rozlytrek film-coated granules. Refer to the Rozlytrek film-coated granules SmPC for prescribing information.

Recommended dosing for paediatric patients > 6 months
<table>
<tr><th>Body surface area (BSA)*</th><th>Once daily dose</th></tr>
<tr><td>≤0.42 m^2</td><td>250 mg/m^2**</td></tr>
<tr><td>0.43 m^2 to 0.50 m^2</td><td>100 mg</td></tr>
<tr><td>0.51 m^2 to 0.80 m^2</td><td>200 mg</td></tr>
<tr><td>0.81 m^2 to 1.10 m^2</td><td>300 mg</td></tr>
<tr><td>1.11 m^2 to 1.50 m^2</td><td>400 mg</td></tr>
<tr><td>≥1.51 m^2</td><td>600 mg</td></tr>
</table>
*BSA categories and recommended dosing in this table are based on closely matching exposures to a target dose of 300 mg/m^2
**To enable dosing increments of 10 mg, capsules prepared as an oral suspension may be used.

Paediatric patients＞ 1 month to≤ 6 months of age
The recommended dose for paediatric patients＞1 month to≤6 months of age is 250 mg/m^2 BSA entrectinib once daily, using capsules prepared as an oral suspension.
Capsules administered as an oral suspension (oral or enteral use) enable dosing increments of 10 mg. The daily dose to be</td></tr>
</table>

	administered should be rounded to the nearest 10 mg increment as described in the SmPC.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: • Each 100 mg hard capsule contains 100 mg entrectinib. • Each 200 mg hard capsule contains 200 mg entrectinib. • Each sachet (of film-coated granules) contains 50 mg entrectinib.
	Proposed: Not applicable.
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
ALT	alanine aminotransferase
aOR	adjusted odds ratio
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BDNF	brain-derived neurotrophic factor
BMD	bone mineral density
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BRS	baroreflex sensitivity
BSA	body surface area
CCOD	clinical cut-off date
CHF	congestive heart failure
CHMP	committee for medicinal products for human use
CI	confidence interval
CIN	cervical intra-epithelial neoplasia
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CP	Child-Pugh
CRC	colorectal cancer
CYP	Cytochrome P450
dmNTS	dorsal medial nucleus tractus solitarius
DXA	dual x-ray absorptiometry
ECG	Electrocardiogram
EEA	European Economic Area
EGFR	epidermal growth factor receptor
EIAED	enzyme inducing antiepileptic drugs,
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	U.S. Food and Drug Administration

Abbreviation	Definition
GI	gastrointestinal
GIST	gastrointestinal stromal tumours
HCC	hepatocellular carcinoma
hERG	human ether-a-go-go-related gene
HLGT	high level group term
HLT	high level term
HR	hazard ratio
KRAS	Kirsten rat sarcoma viral oncogene homolog
LTP	long-term potentiation
MAH	market authorisation holder
MAP	mean arterial pressure
MASC	mammary analogue secretory carcinoma
mDOR	median duration of response
MI	myocardial infarction
mPFS	median progression free survival
MTD	maximum tolerated dose
NCI-ODWG	National Cancer Institute - organ dysfunction working group
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGF	nerve growth factor
NGS	next generation sequencing
NICU	neonatal intensive care unit
NR	not reached
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
OR	odds ratio
ORR	objective response rate
PAES	post-authorization efficacy study
PK	pharmacokinetic
popPK	population pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	preferred term
QTc	corrected QT interval
QTcF	corrected QT interval by Fridericia
RMP	Risk Management Plan

Abbreviation	Definition
ROS1	ROS proto-oncogene 1, receptor tyrosine kinase
RoW	Rest of World
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	system organ class
SRS	stereotactic radiosurgery
TCR	Taiwan Cancer Registry
TKI	tyrosine kinase inhibitor
TMB	tumour mutational burden
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)

SI.1INDICATION(S)

SI.1.1 ADULT AND PAEDIATRIC PATIENTS OLDER THAN ONE MONTH WITH SOLID TUMOURS THAT HAVE A NTRK GENE FUSION (please refer to approved label for full wording)

Incidence and Prevalence

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% of solid tumours were *NTRK* fusion-positive (FoundationCORE® database). This prevalence remains consistent in recently published NGS profiling data from the FoundationCORE® database in which 889 of 295,676 patient samples harboured an *NTRK* gene fusion (prevalence of 0.30%; Westphalen et al. 2021). Previous 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]), and also specifically for paediatric/adolescent patients (0.44%, Pavlick et al. 2017; 0.49%, Chmielecki 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 leukaemia 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 harbour 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 Harbour 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 [a]	≥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 [b]	2L	16.4	5.7	4.0	10.7	Sobrero et al. 2008
	Panitumumab+FOLFIRI [b]	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	Tabernero 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 [c]	≥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	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 [d]	≥2L	4.0	NA	2.6	13.5	Schöffski et al. 2016
	Sunitinib [e]	2L	6.8	NA	24.1	72.7	Demitri et al. 2006
	Regorafenib [e]	≥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 [f]	≥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[g]	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.

[a] In patients with PD-L1 expression on at least 1% of tumour cells.

[b] For patients with RAS wild type tumours.

[c] Patients with HER2-positive advanced/metastatic breast cancer.

[d] For patients with liposarcomas.

[e] Patients with unresectable and/or metastatic gastrointestinal stromal tumours (GIST) after failure of imatinib.

[f] Non-adipocytic STS (excluding liposarcomas).

[g] 59% of patients had at least one previous treatment.

Larotrectinib was approved by the U.S. Food and Drug Administration (FDA) in November 2018 for the treatment of adult and paediatric patients with solid tumours that have an NTRK gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment (US FDA 2018). One year after the approval of larotrectinib, entrectinib was approved for the treatment of adult and paediatric patients 12 years of age and older with solid tumours harbouring an NTRK gene fusion who have no other effective therapies (US FDA 2019). The FDA approved the expansion of the NTRK indication to include paediatric patients over 1 month of age in October 2023 (US FDA 2023).

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.

Use in Pregnancy, Breastfeeding and in Women of Childbearing Potential

It is considered that entrectinib is highly likely to have an adverse effect in the developing foetus based on the pharmacological activity. Based on the findings in animal studies, entrectinib may cause foetal harm when administered to a pregnant woman. Pregnant women, lactating women and women intending to become pregnant have been excluded from the entrectinib development programme. In addition, Section 4.6 (Fertility, pregnancy and lactation) of the Summary of Product Characteristics (SmPC) advises women of child-bearing potential to avoid pregnancy while receiving entrectinib, and for breastfeeding to be discontinued while on treatment. All women of child-bearing potential must use highly effective contraception while on treatment and for at least 5 weeks after stopping treatment as advised by their doctor.

No clinical studies assessing the reproductive and developmental toxicity of entrectinib have been conducted to date and hence there are currently no available data regarding the use of entrectinib during pregnancy. There is no further data on the evidence of pregnancy in patients with a NTRK gene fusion available in the literature.

Adverse Pregnancy Outcomes

- Breast Cancer

A study on 413 patients with early breast cancer receiving chemotherapy during pregnancy, the adverse obstetrical outcomes reported were caesarean delivery (46%) and premature delivery (51%) (Loibl et al. 2012).

A systematic literature review was conducted to identify studies including patients with pregnancy after breast cancer cumulatively until October 2020. A total of 39 studies involving 8,093,401 women from the general population (without breast cancer) and 112,840 patients with breast cancer were included. Women with breast cancer were significantly less likely to have a subsequent pregnancy compared to general population (relative risk, 0.40; 95% CI: 0.32, 0.49). Risks of caesarean section (odds ratio [OR], 1.14; 95% CI: 1.04, 1.25), low birth weight (OR, 1.50; 95% CI: 1.31, 1.73), preterm birth (OR, 1.45; 95% CI: 1.11, 1.88), and small for gestational age (SGA) (OR, 1.16; 95% CI: 1.01, 1.33) were significantly higher in women with breast cancer, particularly in those with previous chemotherapy exposure, compared with the general population (Lambertini et al. 2021).

A retrospective population-based cohort study from Sweden identified 2,870,518 pregnant women without breast cancer (control women) and 331 pregnant women with breast cancer between 1973 and 2002. Incidence of adverse pregnancy outcome in control women vs women with breast cancer were pregnancy bleeding (1% vs 1%), delivery complications (35% vs 52%), small for gestational age (1% vs 3%), stillbirth (0.36% vs 0.60%), low birth weight (1% vs 2%), foetal malformation (4% vs 7%). Women with breast cancer were at increased risk for delivery complications (adjusted odds ratio [aOR] 1.5, 95% CI: 1.2, 1.9), caesarean section (aOR 1.3, 95% CI: 1.0, 1.7), preterm birth (< 32 weeks) (aOR 3.2, 95% CI: 1.7, 6.0), infants with low gestational age (aOR 3.20, 95% CI: 1.70, 6.03), low birth weight (aOR 2.9, 95% CI: 1.4, 5.8), and foetal malformation (aOR 1.68, 95% CI: 1.11, 2.54), adjusted for maternal age, parity and year of delivery (Dalberg et al. 2006). A similar study from South Korea reported the incidence of adverse pregnancy outcomes in control women vs breast cancer survivors as preterm delivery (8.2% vs 8.5%), miscarriages (14.6% vs 15%), preterm labour (8.9% vs 11.7%), obstetric haemorrhage (6.2% vs 6.2%), hydramnios/oligoamines (4.5% vs 5.0%). Preterm labour was found to occur more frequently in breast cancer survivors (aOR 1.33, 95% CI: 1.06, 1.65). There were no differences between the subject groups regarding risk for preeclampsia, obstetric haemorrhage, miscarriage, or hydramnios/oligoamines (Lee et al. 2019).

In a multicentre cohort study of 1170 pregnant women (1996-2016), 462 women were diagnosed with breast cancer. Among these, 428 women presented with adverse obstetric outcome that included preterm births (39.4%), miscarriages (1.3%), termination of pregnancy (5.6%), still birth and maternal death during pregnancy (<1% each) (de Hann et al. 2018).

A retrospective study included 126, 646 females with first invasive cancer during child-bearing age using data from Taiwan Cancer Registry (TCR) between 2001-2015. Among these 512 women were diagnosed with cancer during pregnancy. The risk of death found to be high in patients with breast cancer during the pregnancy (hazard ratio [HR] 2.31; 95% CI: 1.71, 3.12) (Li et al. 2020).

- Melanoma

In an European observational cohort study, 59 patients accounted for 60 pregnancies between 1994 and 2015. Obstetric outcomes were reported in 53 (88.3%) pregnancies. There were nine preterm babies (18%), and caesarean section was carried out in six (12.2%) cases. Three patients chose to terminate their pregnancies, while one patient and the foetus died in the cohort. Three (5.4%) full-term neonates were admitted for an infection, Rhesus D haemolytic disease of the newborn and respiratory insufficiency (de Haan et al. 2017). In an international cohort study of 1170 pregnant patients diagnosed with cancer between 1996 and 2016, 46 had melanoma. Among melanoma patients (43 patients with available with obstetric outcomes), the obstetrics outcomes reported were preterm birth (6.5%), termination of pregnancy (4.3%) and maternal death during pregnancy (2.2%) (de Hann et al. 2018). In a large, population-based study of pregnant women in California from 1991 to 1999 with malignant melanoma, maternal and neonatal outcomes reported were caesarean delivery (29.7%), pre-eclampsia (1.3%), preterm delivery (7.7%) and low birth weight (4.1%) (O'Meara et al. 2005). In Australia between 1994 and 2008, the pregnancy outcomes reported in melanoma patients were: preterm birth (5.6%), caesarean section (27.7%), and small for gestational age (6.2%) (Bannister-Tyrrell et al. 2015).

A retrospective study included 126, 646 women of child-bearing age using data from TCR between 2001-2015. Among these 512 cases of women were diagnosed with cancer during pregnancy. The risk of death found to be high in patients with skin cancer diagnosed during pregnancy (HR, 2.84; 95% CI: 0.91, 8.89) (Li et al. 2020).

- Cervical cancer and ovarian cancer

Cervical intra-epithelial neoplasia (CIN) typically occurs in young women of reproductive age. A meta-analysis of 15 studies examining pregnancy outcomes in over 38,000 female CIN patients reported the adverse pregnancy outcomes in the population which included miscarriage (3.12%), ectopic pregnancies (0.86%) and pregnancy termination (8.3%) (Kyrgiou et al. 2015). A large population-based study using data from Swedish Medical Birth Register compared obstetric outcomes in women with CIN3 to general population. The pregnancy outcome in CIN3 population and general population were preterm births (9.5% vs. 4.9%); small for gestational age (2.9% vs 2.7%), intrauterine foetal death (0.39% vs. 0.38%) and early neonatal death (0.33% vs 0.18%). Compared with the matched general population, women with a prior CIN3 diagnosis were generally more likely to have an adverse pregnancy outcome. The associations were stronger among women with lower education, higher parity, and lower pre-pregnancy BMI than among their respective counterparts (He et al. 2022). In a meta-analysis of 20 studies examining pregnancy outcomes in 85,211 pregnant women with CIN, 16.0% underwent caesarean section and 3.9% developed (preterm) premature rupture of membrane. The risk of spontaneous preterm birth (less than 37 weeks) and preterm birth (less than 32 weeks) were 4.6% and 2.31% respectively. Perinatal mortality was found to be 1.2% (Danhof et al. 2015).

In a multicentre cohort study of 1170 pregnant women (1996-2016), a total of 147 women had cervical cancer and 88 women had ovarian cancer. Out of these, 140 women with cervical cancer presented with adverse obstetric outcomes that included preterm births (49%), miscarriages (1.4%), termination of pregnancy (14.3%) and still birth (1.4%). The adverse obstetric outcomes in 83 ovarian cancer women included; preterm births (24%), miscarriages (3.4%) and termination of pregnancy (3.4%) (de Haan et al. 2018).

- Other cancers

Limited information was available for adverse pregnancy outcomes in a woman with thyroid cancer. A retrospective study using medical records of a hospital enrolled 125 women with thyroid cancer with distant metastasis between 2005-2021. Among these women, 28 women became pregnant with 40 live births. Among 40 live births, the incidence of premature birth was 5.0%, external abnormally was 5.0% and small for gestational age was 2.5%. Other pregnancy outcomes were miscarriage (11.2%) and induced abortion (0.8%). (Yamazaki et al. 2021).

In a multicentre cohort study of 1170 pregnant women (1996-2016), 49 women were diagnosed with gastrointestinal (GI) cancer. Out of these, 44 women presented with adverse obstetric outcome that included preterm births (59%), miscarriages (4%), termination of pregnancy (8%), still births (4%) and maternal death during pregnancy (2%). In terms of neonatal outcomes, GI cancer was associated with neonatal intensive care unit (NICU) admission (OR, 7.13; 95% CI: 2.86, 17.7]) as compared to breast cancer patients (taken as reference). In the same study, 37 women and 19 women were diagnosed with thyroid cancer and brain cancer respectively. All these women presented adverse obstetric outcomes that included preterm births (3% vs. 43%), termination of pregnancy (11% vs 9.5%) and maternal death during pregnancy (0% vs. 9.5%) (de Haan et al. 2018).

Limited information was available for hepatocellular carcinoma and urothelial carcinoma in pregnant women. Reported cases of hepatocellular carcinoma (HCC) in pregnancy are largely isolated and highly scattered. Thus, the effect of pregnancy on the prognosis of patients with HCC and the risk factors of developing HCC in pregnancy are not well documented.

The rarity of HCC in pregnancy results from a combination of three factors: the male predominance of HCC, the late age at which the tumour usually presents in women, and decreased fertility in women with advanced cirrhosis (hepatitis is a predisposing factor for HCC development) (Lau et al. 1995). Bladder tumours in pregnancy are an extremely rare diagnosis. Recently, a study reported that approximately 50 cases have been published as single case reports or case series for pregnancy in bladder cancer patients, including all histologic variants (Rojas et al. 2021).

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 United States and European Union, 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.

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[a]	387,913	23.1[a]	497,283[a]

n = Number of patients; U.S. = United States

[a] 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 ROS proto-oncogene 1, receptor tyrosine kinase (ROS1), anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS), and v-raf murine sarcoma viral oncogene homolog B1 (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 oedema) and chronic complications of delayed haemorrhage 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% CI: 56%, 82%). The median duration of response (mDOR) 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® 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.

Use in Pregnancy, Breastfeeding and in Women of Childbearing Potential

It is considered that entrectinib is highly likely to have an adverse effect in the developing foetus based on the pharmacological activity. Based on the findings in animal studies, entrectinib may cause fetal harm when administered to a pregnant woman. Pregnant women, lactating women and women intending to become pregnant have been excluded from the entrectinib development programme. In addition, Section 4.6 (Fertility, pregnancy and lactation) of the SmPC advises women of child-bearing potential to avoid pregnancy while receiving entrectinib, and for breastfeeding to be discontinued while on treatment. All women of child-bearing potential must use highly effective contraception while on treatment and for at least 5 weeks after stopping treatment as advised by their doctor.

No clinical studies assessing the reproductive and developmental toxicity of entrectinib have been conducted to date and hence there are currently no available data regarding the use of entrectinib during pregnancy. There is no further data on the evidence of pregnancy in patients with a ROS1 positive NSCLC available in the literature.

Adverse Pregnancy Outcomes

Lung cancer during pregnancy remains a rather uncommon condition with less than 70 cases published until 2016. Non-small cell lung carcinoma is the commonest type accounting for about 85% of all cases (mainly adenocarcinoma). Overall survival rates are low. Chemotherapy and/or targeted treatment have been used with poor outcomes. The disease has been also found to affect the products of conception with no short- or long-term consequences for the neonate (Mitrou et al. 2016). A nationwide cohort study from Denmark included 1857 pregnant women with lung cancer and 18,244 pregnant matched cancer-free controls followed until 2017. The prevalence of single pregnancy loss (cases vs control) had been reported to be in 18.4% vs 18.1%, two pregnancy losses in 3.5% vs 3.9% and $\geq$ 3 pregnancy losses in 1.5% vs 1.5% of the total pregnancies (Mikkelsen et al. 2019).

A retrospective study included 126, 646 women of child-bearing age using data from TCR between 2001-2015. Among these, 512 cases of women were diagnosed with cancer during pregnancy. The risk of death found to be high in patients with lung cancer during the pregnancy (HR, 2.02; 95% CI: 1.05, 3.89) (Li et al. 2020).

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).

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

Comorbid condition	Prevalence		
	People without cancer, ≥66 years [a] (%)	All stages, SEER-Medicare, ≥66 years [a] (%)	Metastatic, U.S. VA, ≥65 years [b] (%)
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.

[a] Edwards et al. 2014.

[b] Wang et al. 2012.

PART II: MODULE SII – NONCLINICAL PART OF THE SAFETY SPECIFICATION

The toxicology programme 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-foetal 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 haematological 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
Neurological Findings	
CNS clinical signs were observed in rats at ≥100 mg/kg/day (C_{max} ≥3.0 µM) and in dogs at ≥60 mg/kg/day (C_{max} ≥3.0 µM) in the 14-day and the 4-week (2×2 cycles) studies. In juvenile rats, CNS signs were observed at ≥8 mg/kg/day (C_{max} ≥0.614 µM). 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 C_{max} 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.	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. 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%), dysaethesia 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. 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.
Effects on Skin	
Entrectinib caused skin lesions in rats, juvenile rats and dogs at exposures ≥0.1 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 ≥7.5 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.	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 (q_adr_t_ae_medcon_SE); (q_smpc_t_ae_medcon_3_SE). Rash is included as ADR in the Undesirable effects section (Section 4.8) of the entrectinib SmPC.

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

Key Safety Findings	Relevance to Human Use
Effects on Red Blood Cells	
Decreased RBC mass were observed in both species with histopathological correlates of increased extramedullary haematopoiesis in spleen and liver and changes in bone marrow. These findings were observed in rats, juvenile rats and dogs at exposures ≥0.1 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.	Hematologic events have been observed in patients treated with entrectinib in clinical trials. The most frequently reported hematologic toxicities were anaemia and neutropenia (PTs of neutrophil count decreased and neutropenia). Anaemia of all grades and Grade 3 and above were reported in 28.2% and 9.7% of patients, respectively. Neutropenia AEs of all grade and Grade ≥3 were reported in 11.3% and 4.4% of patients, respectively (Entrectinib SmPC). 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. Anaemia 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.
Gastrointestinal Effects	
Entrectinib caused GI effects in dogs and included dose-limiting vomiting and diarrhoea, microscopically erosion/ulcer of anal squamous epithelium and/or neutrophil infiltrates in rectum were observed. These findings were observed in dogs at exposures ≥0.1 fold the human exposure by AUC at recommended dose.	AEs of gastrointestinal disorders were a common AE observed in entrectinib clinical trials; the most common events reported (by PT) were constipation (42.9%), diarrhoea (33.5%), nausea (32.1%) and vomiting (23.2%). In addition, abdominal pain (11.1%) has been observed (Entrectinib SmPC). All of the events above are considered ADRs in the Undesirable effects section (Section 4.8) of the entrectinib SmPC.
Cardiovascular System	
QTc prolongation was observed in dogs at exposures ≥0.1 fold the human exposure by C_{max} at recommended dose. In vitro, entrectinib inhibited hERG with an IC_{50} of 0.6 µM as a free drug.	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.

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

Key Safety Findings	Relevance to Human Use
Increases in QT/QTc intervals were noted in repeat-dose studies at ≥15 mg/kg/day. No changes in QT/QTcF interval were observed in single dose acute telemetry studies up to 300 mg/kg.	QT prolongation is considered to be important identified risk (see Section SVII.3.1.1.2) and is included in the Posology and method of administration (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	
Liver findings were observed in rats and dogs at exposures ≥0.1 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 (≥MTD) included vacuolation of hepatocytes and bile duct epithelium, and hepatocellular necrosis in rats at ≥200 mg/kg/day, and hepatocellular necrosis and increased pigmented macrophages at ≥60 mg/kg/day in dogs.	The nonclinical data from two animal species at clinically relevant exposures indicate that hepatobiliary laboratory test elevations may occur in patients receiving entrectinib. 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). AST increased and ALT increased are ADRs in the Undesirable effects section (Section 4.8) of the entrectinib SmPC.
Ocular Effects	
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.	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 (≥2% 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. The only Grade 3 eye disorder events were diplopia reported in 2 patients, which resolved in both cases.

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

Key Safety Findings	Relevance to Human Use
	Vision blurred (including diplopia, vision blurred and visual impairment) is an ADR in the Undesirable effects section (Section 4.8) of the entrectinib SmPC. Patients who experience these events are instructed not to drive or use machines until the symptoms resolve.
Reproductive and Developmental Toxicity	
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).	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. 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. Entrectinib is not intended to be used during pregnancy or breastfeeding.

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

Key Safety Findings	Relevance to Human Use
Genotoxicity	
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.	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.
Carcinogenicity	
No carcinogenicity studies have been conducted with entrectinib and none are planned.	Entrectinib is indicated for patients with advanced cancers; therefore, no carcinogenicity studies have been performed to establish its carcinogenic potential.
Paediatric Effects	
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 haematological 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 neurobehavioral 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.	The safety of entrectinib in paediatric patients has been evaluated in patients with solid tumours in the CO40778 (STARTRK-NG), GO40782 (STARTRK-2), and BO41932 (TAPISTRY) studies. Where reported, the nature and severity of events observed in paediatrics was similar to that of the adult population. The incidence of the following adverse events were ≥5% 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, rhinorrhoea, tachypnoea, decreased appetite, dehydration, hypokalaemia, hyperglycaemia, hypophosphataemia, hypocalcaemia, hypernatraemia, increased appetite, hypermagnesaemia, hyperphosphataemia, lung infection, pharyngitis, pruritus, hyperhidrosis, anaemia, photophobia, and eye pain.

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

Key Safety Findings	Relevance to Human Use
	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. 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)

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 CO40778 (STARTRK-NG, RXDX-101-03) in young adults, adolescents and children > 2 months of age; as well as 2 paediatric patients in GO40782 (herein referred to as the 'initial paediatric population' for readability) see Table 6.

Data have been analysed 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.

An additional dataset has been analysed using a population of paediatric patients (n=76) from studies GO40778 (STARTRK-NG), BO41932 (TAPISTRY), and GO40782 (STARTRK-2) with a CCOD of 2 August 2022. This population is referred to herein as the 'expanded paediatric population'.

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 sets

- **Initial paediatric analysis set (CCOD 31 October 2018):** Patients from the CO40778 (STARTRK-NG), and GO40782 (STARTRK-2) studies in the safety population (n=29).

  The adult and paediatric analysis datasets described above were defined by the age of patients at initial trial enrolment; 2 patients <18 years were enrolled in GO40782 and were included in the paediatric analysis dataset, and 2 patients >18 years were enrolled in CO40778 and were included in the adult analysis dataset (see Table 6 for additional details).

- **Expanded paediatric analysis set (CCOD 2 August 2022):** Patients under 18 years of age enrolled in studies GO40778, BO41932, and GO40782 who received at least one dose of entrectinib up to a CCOD of 2 August 2022 (n=76).

The dose received by patients was not always 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

Study	Study Design	Population	Dose, Route, Regimen, and Formulation [a]	Patients Evaluable for Safety (n)
ALKA-372-001 (ALKA)	First-In-Human, Phase I, single-arm, open-label, multicentre, 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: Schedule A: 100, 200, 400, 800, 1200, or 1600 mg/m^2/day, 4 days on treatment and 3 days off treatment for 3 weeks followed by a 7-day rest period in 4-week cycles Schedule B: 200, 400 mg/m^2/day in a continuous daily dosing regimen in 4-week cycles Schedule C: 400 or 800 mg/m^2/day 4 days on treatment and 3 days off treatment in 4-week cycles	60 (CCOD 31 October 2018)
RXDX-101-01 (STARTRK-1)	Phase I, single-arm, open-label, multicentre, 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: – 100, 200, 400 mg/m^2/day (BSA based); F1 – 800 mg/day (flat) F1 – 600 mg/day if BSA $\leq$ 1.85 m^2 F1; 800 mg/day if BSA $>$ 1.85 m^2 F1 – 600 mg/day (flat) F1 and F2A	83 (CCOD 31 October 2018)

Table 6 Overview of Studies Contributing to the Safety Population

Study	Study Design	Population	Dose, Route, Regimen, and Formulation [a]	Patients Evaluable for Safety (n)
GO40782 (RXDX-101-02 STARTRK-2) [b]	Phase II, single-arm, open-label, multicentre	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[b] (CCOD 31 October 2018)
		Paediatric patients with locally advanced or metastatic solid tumours that harbour *an NTRK1/2/3, ROS1, or ALK* gene rearrangement	600 mg, Oral, QD, 4-week cycle	2[e] (CCOD 2 August 2022)
CO40778 (RXDX-101-03, STARTRK-NG) [c]	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	Phase I Oral, QD F1 (3 patients received F2B), in a continuous daily dosing regimen Dosing as per nomogram ranging from 250 to 750 mg/m^2/day orally Phase II F06: Doses ranging from 100 to 600 mg PO or from 20 to 600 mg as aqueous suspension via NG/gastric tube or orally via a syringe daily F1: Doses ranging from 300 to 600 mg PO daily Coated granules: Doses ranging from 100 to 600 mg PO daily	29[b,c,d] (CCOD 31 October 2018) 68[f] (CCOD 2 August 2022)

Table 6 Overview of Studies Contributing to the Safety Population

Study	Study Design	Population	Dose, Route, Regimen, and Formulation [a]	Patients Evaluable for Safety (n)
BO41932 (TAPISTRY)	Phase II, global, multicentre, open-label	Paediatric patients with *NTRK1/2/3* or *ROS1* fusion-positive tumours	600 mg PO daily for patients with BSA ≥1.51 m^2 Doses ranging from 100 to 600 mg PO daily for patients with BSA <1.51 m^2 F06: Doses ranging from 100 to 600 mg PO or from 20 to 600 mg as aqueous suspension via NG/gastric tube or orally via a syringe daily Coated granules: Doses ranging from 100 to 600 mg PO daily	6 (CCOD 2 August 2022)
Total Patients				**504**

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

[a] F1, F2A and F2B refer to specific formulations used in the clinical development programme, respectively.

[b] Two paediatric 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)

[c] Two adult patients 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).

[d] Sixteen patients were enrolled in the Phase I dose escalation and 13 additional patients were enrolled in the Phase 2 extension phase.

[e] Two paediatric patients were enrolled in the study as of 2 August 2022. These patients received 600 mg entrectinib orally QD, on a 4-week cycle

[f] A total of 68 patients were enrolled in the study (comprising both phases) as of 2 August 2022.

Duration of Exposure

As of a CCOD of 31 October 2018, the entrectinib safety population provided 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 initial paediatric population (CCOD 31 October 2018), more children (62.1% [n=18]) were exposed to entrectinib for <6 months compared to adults (51.6% [n=245]). In addition, the initial paediatric population only accounted for 13.2 person-years of exposure versus 73.1 person-years of exposure in the expanded paediatric population (CCOD 2 August 2022, n=76). More patients in the expanded paediatric population were exposed to entrectinib for<6 months (42.1% [n=32]) than any other exposure duration (Table 8).

Exposure by Age Group and Gender

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 9). Female patients had 196.1 patient-years of exposure vs. 127.8 patient-years in male patients.

In the initial paediatric population, 55.2% (n=16) of patients were male and 44.8% (n=13) were female. The largest group (48.3% [n=14]) of patients were 6–<12 years of age, followed by 24.1% (7 patients each) for the groups aged 12–<18 years and 2–<6 years. One patient (3.4%) was aged between 0–<2 (Table 9).

In the expanded paediatric population (CCOD 2 August 2022, n=76), 48.7% (n=37) of patients were male and 51.3% (n=39) patients were female. The largest age group of these patients (39.5% [n=30]) were 6–<12 years of age, followed by 25.0% (19 patients) aged 2–<6 years, 18.4% (14 patients) between 0–<2 years, and 17.1% (13 patients) aged 12–<18 years (Table 10).

Exposure by Dose

Exposure data were calculated according to a patient's actual treatment received and include 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 11). 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 initial 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 11).

In the expanded paediatric population (CCOD 2 August 2022, n=76), 23.7% (n=18) of patients received a dose of 400 mg, with 18.4% (n=14) and 15.8% (n=12) of patients receiving 300 mg and 200 mg, respectively. The lowest dose received was 100 mg (3.9% [n=3]) and the highest dose was 10800 mg (1.3% [n=1]) (Table 12).

Exposure by Racial Origin

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. In the initial 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 13).

In the expanded paediatric population (CCOD 2 August 2022, n=76), the largest proportion of patients [67.1% (n=51)] were White; 19.7% (n=15) were Asian; and 6.6% (n=5) were Black or African American and 6.6% (n=5) of Other race (Table 14).

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 (N=113)	ADULT-OTHER (N=152)	ADULT-ROS1 NSCLC (N=210)	ADULT-TOTAL (N=475)	PEDIATRIC (N=29)	TOTAL (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 Duration of Exposure (Expanded Paediatric Population)

Exposure, by Duration of Exposure (Months), Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

	NTRK - Pediatric (N=39)	ROS1 - Pediatric (N=19)	Other - Pediatric (N=18)	Total - Pediatric (N=76)
Counts of Patients in Treatment duration groups				
0 to <6 months	10 (25.6%)	7 (36.8%)	15 (83.3%)	32 (42.1%)
6 months to <12 months	9 (23.1%)	5 (26.3%)	1 (5.6%)	15 (19.7%)
12 months to <18 months	11 (28.2%)	2 (10.5%)	0	13 (17.1%)
18 months to <24 months	3 (7.7%)	2 (10.5%)	0	5 (6.6%)
>=24 months	6 (15.4%)	3 (15.8%)	2 (11.1%)	11 (14.5%)
Treatment duration groups in person time (years)				
Total	45.5	18.3	9.3	73.1
0 to <6 months	3.2	1.6	2.6	7.3
6 months to <12 months	6.8	3.6	0.9	11.4
12 months to <18 months	13.0	2.3	NE	15.3
18 months to <24 months	5.2	3.9	NE	9.1
>=24 months	17.4	6.8	5.8	30.0

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.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

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Table 9 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: Age group (years)	No. of Patients			Person Year		
	Male	Female	Total	Male	Female	Total
Total						
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
Total	227 (45.0%)	277 (55.0%)	504 (100%)	127.8	196.1	324.0
NTRK-Adult						
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
Total	55 (48.7%)	58 (51.3%)	113 (100%)	31.8	41.5	73.3
ROS1 NSCLC-Adult						
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
Total	80 (38.1%)	130 (61.9%)	210 (100%)	60.8	111.8	172.6

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 9 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: Age group (years)	No. of Patients			Person Year		
	Male	Female	Total	Male	Female	Total
Other-Adult						
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
Total-Adult						
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
Pediatric						
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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Table 10 Exposure by Age Group and Gender (Expanded Paediatric Population)

Exposure by Age Group and Gender, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

Basket Group: Age group (years)	Patients			Person Year		
	Male	Female	Total	Male	Female	Total
Total - Pediatric						
0-<2	7 (9.2%)	7 (9.2%)	14 (18.4%)	9.9	10.6	20.5
2-<6	8 (10.5%)	11 (14.5%)	19 (25.0%)	6.0	13.5	19.5
6-<12	14 (18.4%)	16 (21.1%)	30 (39.5%)	7.2	14.5	21.7
12-<18	8 (10.5%)	5 (6.6%)	13 (17.1%)	3.9	7.5	11.4
Total	37 (48.7%)	39 (51.3%)	76 (100%)	27.0	46.1	73.1
NTRK - Pediatric						
0-<2	6 (15.4%)	5 (12.8%)	11 (28.2%)	8.6	8.2	16.8
2-<6	6 (15.4%)	8 (20.5%)	14 (35.9%)	4.6	11.1	15.7
6-<12	3 (7.7%)	6 (15.4%)	9 (23.1%)	1.9	5.9	7.7
12-<18	2 (5.1%)	3 (7.7%)	5 (12.8%)	3.1	2.2	5.2
Total	17 (43.6%)	22 (56.4%)	39 (100%)	18.1	27.4	45.5
ROS1 - Pediatric						
0-<2	1 (5.3%)	2 (10.5%)	3 (15.8%)	1.3	2.4	3.7
2-<6	2 (10.5%)	1 (5.3%)	3 (15.8%)	1.4	2.0	3.4
6-<12	4 (21.1%)	6 (31.6%)	10 (52.6%)	3.2	5.4	8.7
12-<18	2 (10.5%)	1 (5.3%)	3 (15.8%)	0.2	2.3	2.5
Total	9 (47.4%)	10 (52.6%)	19 (100%)	6.2	12.1	18.3
Other - Pediatric						
0-<2	0	0	0	NE	NE	NE
2-<6	0	2 (11.1%)	2 (11.1%)	NE	0.5	0.5
6-<12	7 (38.9%)	4 (22.2%)	11 (61.1%)	2.1	3.2	5.3
12-<18	4 (22.2%)	1 (5.6%)	5 (27.8%)	0.6	3.0	3.6
Total	11 (61.1%)	7 (38.9%)	18 (100%)	2.7	6.6	9.3

Person-time is defined as the sum of the exposure time (from first to last administration of study drug) for every patient.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

Program: root/clinical_studies/RO7102122/share/pool_aco_2022/prod/program/t_ex_rmp_age.sas
Output: root/clinical_studies/RO7102122/share/pool_aco_2022/prod/output/t_ex_rmp_age_AGE18_SE_RMP.out
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Table 11 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 (N=113)	ADULT-OTHER (N=152)	ADULT-ROS1 NSCLC (N=210)	ADULT-TOTAL (N=475)	PEDIATRIC (N=29)	TOTAL (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.

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
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Table 11 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

Dose of Exposure	ADULT-NTRK (N=113)	ADULT-OTHER (N=152)	ADULT-ROS1 NSCLC (N=210)	ADULT-TOTAL (N=475)	PEDIATRIC (N=29)	TOTAL (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>=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
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Table 12 Exposure by Dose (Expanded Paediatric Population)

Exposure, by Exposure Dose, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

	NTRK - Pediatric (N=39)	ROS1 - Pediatric (N=19)	Other - Pediatric (N=18)	Total - Pediatric (N=76)
Dose of Exposure				
100mg	2 (5.1%)	1 (5.3%)	0	3 (3.9%)
150mg	1 (2.6%)	1 (5.3%)	0	2 (2.6%)
200mg	9 (23.1%)	1 (5.3%)	2 (11.1%)	12 (15.8%)
300mg	6 (15.4%)	5 (26.3%)	3 (16.7%)	14 (18.4%)
400mg	9 (23.1%)	5 (26.3%)	4 (22.2%)	18 (23.7%)
500mg	1 (2.6%)	1 (5.3%)	2 (11.1%)	4 (5.3%)
600mg	5 (12.8%)	3 (15.8%)	3 (16.7%)	11 (14.5%)
700mg	1 (2.6%)	1 (5.3%)	2 (11.1%)	4 (5.3%)
900mg	0	0	1 (5.6%)	1 (1.3%)
1100mg	0	0	1 (5.6%)	1 (1.3%)
1620mg	1 (2.6%)	0	0	1 (1.3%)
2430mg	1 (2.6%)	0	0	1 (1.3%)
5400mg	1 (2.6%)	0	0	1 (1.3%)
6000mg	1 (2.6%)	0	0	1 (1.3%)
6800mg	1 (2.6%)	0	0	1 (1.3%)
10800mg	0	1 (5.3%)	0	1 (1.3%)
Dose of Exposure in person time (years)				
Total	45.5	18.3	9.3	73.1

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.
Dose of Exposure is defined as the highest dose received per patient.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

Program: root/clinical_studies/RO7102122/share/pool_aco_2022/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO7102122/share/pool_aco_2022/prod/output/t_ex_rmp_AGE18_SE_BYDOS_RMP.out
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Table 12 Exposure by Dose (Expanded Paediatric Population) (cont.)

Exposure, by Exposure Dose, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

	NTRK - Pediatric (N=39)	ROS1 - Pediatric (N=19)	Other - Pediatric (N=18)	Total - Pediatric (N=76)
Dose of Exposure				
100mg	3.0	0.2	NE	3.2
150mg	1.3	1.3	NE	2.6
200mg	7.7	0.5	0.3	8.5
300mg	12.3	4.3	0.6	17.2
400mg	12.2	5.9	0.3	18.5
500mg	0.7	2.0	0.6	3.3
600mg	4.6	2.7	3.3	10.5
700mg	0.9	1.0	1.1	3.0
900mg	NE	NE	0.1	0.1
1100mg	NE	NE	3.0	3.0
1620mg	0.3	NE	NE	0.3
2430mg	0.2	NE	NE	0.2
5400mg	1.2	NE	NE	1.2
6000mg	0.5	NE	NE	0.5
6800mg	0.7	NE	NE	0.7
10800mg	NE	0.3	NE	0.3

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.
Dose of Exposure is defined as the highest dose received per patient.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

Program: root/clinical_studies/RO7102122/share/pool_aco_2022/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO7102122/share/pool_aco_2022/prod/output/t_ex_rmp_AGE18_SE_BYDOS_RMP.out
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Table 13 Exposure by Racial Origin

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

	ADULT-NTRK (N=113)	ADULT-OTHER (N=152)	ADULT-ROS1 NSCLC (N=210)	ADULT-TOTAL (N=475)	PEDIATRIC (N=29)	TOTAL (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
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Table 14 Exposure by Racial Origin (Expanded Paediatric Population)

Exposure, by Race, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

	NTRK - Pediatric (N=39)	ROS1 - Pediatric (N=19)	Other - Pediatric (N=18)	Total - Pediatric (N=76)
Counts of Patients by Race				
Asian	12 (30.8%)	3 (15.8%)	0	15 (19.7%)
Black or African American	1 (2.6%)	1 (5.3%)	3 (16.7%)	5 (6.6%)
White	21 (53.8%)	15 (78.9%)	15 (83.3%)	51 (67.1%)
Other	5 (12.8%)	0	0	5 (6.6%)
Treatment duration in person time by Race (years)				
Total	45.5	18.3	9.3	73.1
Asian	9.9	1.0	NE	10.9
Black or African American	2.2	0.3	0.5	3.0
White	27.4	17.1	8.9	53.4
Other	5.9	NE	NE	5.9

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.
'Other' includes 'Other' from ST-NG (CO40778), 'Unknown' from TAPISTRY (BO41932), and 'Other' and 'Not Reported' from ST-02 (GO40782).

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

Program: root/clinical_studies/RO7102122/share/pool_aco_2022/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO7102122/share/pool_aco_2022/prod/output/t_ex_rmp_AGE18_SE_BYRACE_RMP.out
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PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
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 [a].	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.
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.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Patients with inadequate hepatic function.	Unlikely to be able to tolerate entrectinib therapy.	No	A dedicated clinical study (Study GP41174) investigating the effect of impaired hepatic function on the pharmacokinetics of entrectinib has been completed. Refer to Section SVII.2 for more details on study results. No dose adjustment is recommended for patients with hepatic impairment. The recommendation and study results have been added to sections 4.2 and 5.2 of the SmPC, respectively.
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. 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. This information has been captured adequately in the SmPC.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
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. Based on animal studies and its mechanism of action, entrectinib may cause foetal harm when administered to a pregnant woman. It is not known whether entrectinib is excreted in human milk. A risk to the breast-fed child cannot be excluded.	No	Section 4.6 (Fertility, pregnancy and lactation) of the SmPC advises women of child-bearing potential to avoid pregnancy while receiving entrectinib. Section 4.6 (Fertility, pregnancy and lactation) of the SmPC advises breastfeeding 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 SVII3.1.1.1 and SVII3.1.1.2, 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 SVII3.1.1.2).
History of additional risk factors for torsade de pointes.	To minimise the risk of QTc prolongation in these patients.	No	QT prolongation is an important identified risk (see Section SVII3.1.1.2).
Peripheral neuropathy Grade ≥ 2.	TRK receptors are involved with neuronal development and maintenance; as such, central and	No	Given the life-threatening nature of the proposed indications, treatment with entrectinib should be an option for such patients. No specific warning

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
	peripheral neurologic events are expected.		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 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.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
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 SVII.3.1.2.1).
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.

[a] Systemic progressors were allowed in the Phase I studies.

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

The clinical trial development programme 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 ≥ 1/1,000 to < 1/100), rare (≥ 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 programme, 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 initial paediatric population, 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 9). Additional evidence for paediatric patients is provided from studies CO40778 (STARTRK-NG), BO41932 (TAPISTRY), and GO40782 (STARTRK-2) through a CCOD of 2 August 2022. The 76 patients in this expanded paediatric population were exposed for a total of 73.1 patient-years, and most commonly (42.1%) exposed for 0–6 months. 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 programme. 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 PROGRAMMES

Information available for use of entrectinib in populations typically under-represented in the clinical development programme is provided in Table 15; additional details for use in pregnancy and lactation are presented in Use in Pregnancy and Lactation.

Table 15 Exposure of Special Populations Included or Not in Clinical Trial Development Programme

Type of Special Population	Exposure
Pregnant women	No exposure available as not included in the clinical development programme.
Breastfeeding women	No exposure available as not included in the clinical development programme.
	Patients with relevant co-morbidities:
Patients with hepatic impairment	In Study GP41174, 38 subjects were enrolled and dosed with entrectinib. The subjects (N = 38) were classified according to both the Child-Pugh (CP) classification, and the National Cancer Institute-Organ Dysfunction Working Group (NCI-ODWG) classification, see below [a]. Distribution of subjects (N = 38) according to the CP classification: Normal-CP: n = 8 Mild hepatic impairment-CP: n = 7 Moderate hepatic impairment-CP: n = 12 Severe hepatic impairment-CP: n = 11 Distribution of subjects (N = 38) according to the NCI-ODWG classification: Normal-NCI-ODWG: n = 17 Mild hepatic impairment-NCI-ODWG: n = 6 Moderate hepatic impairment-NCI-ODWG: n = 9 Severe hepatic impairment-NCI-ODWG: n = 6 Further information on the Pharmacokinetic data are provided in Section SVII.2.

Table 15 Exposure of Special Populations Included or Not in Clinical Trial Development Programme

Type of Special Population	Exposure
Patients with renal impairment	No exposure available as not included in the clinical development programme.
Patients with cardiovascular impairment	No exposure available as not included in the clinical development programme.
Population with relevant different ethnic origin [b]	See Table 13
Other: Paediatric patients	See Table 9

[a] There was an overlap of subjects between the CP and NCI-ODWG classification.

[b] All ethnicities were represented, and the safety profiles are not expected to be different between ethnicities.

[c] Exposure by race.

Use in Pregnancy and Lactation

In an embryo-foetal development study in rats, maternal toxicity (decreased body weight gain and food consumption) and foetal malformations (including body closure defects and malformations of the vertebrae and ribs) were observed. Further information on the main toxicities of entrectinib is available in Part II: Module SII. Based on this, in addition to animal studies and its mechanism of action, entrectinib may cause foetal harm when administered to pregnant women.

In addition, the risk to the breastfed child cannot be excluded as it is not known whether entrectinib or its metabolites are excreted in human breast milk.

Therefore, pregnant and lactating women were excluded from the entrectinib development programme; as a result, there is no available data from the clinical trial development programme on the use of entrectinib in these patients.

In ongoing clinical trials, women of childbearing potential should undergo medically supervised pregnancy testing prior to initiating entrectinib therapy. Women of childbearing potential must also remain abstinent or use highly effective contraceptive methods (failure rate of $<1\%$ per year) during treatment and for 5 weeks following the final dose of entrectinib.

Summary Tabulations of Prospective and Retrospective Individual Case Safety Reports on Pregnancy are presented in Annex 7C of the RMP.

PART II: MODULE SV – POST-AUTHORISATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method Used to Calculate Exposure

The data presented below are derived from the Entrectinib Periodic Benefit-Risk Evaluation Report (PBRER 1130773) with data lock point (DLP) of 17 June 2024.

Entrectinib received the marketing authorisation in Japan in June 2019 and in the United States 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 United States 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 adult daily dose of entrectinib in ROS1-positive metastatic NSCLC patients and NTRK+solid tumour patients is 600 mg orally once daily. The duration of therapy is informed by median progression-free survival (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 25% and 75% for NTRK positive and ROS1 positive, respectively.

SV.1.2 Exposure

Since the IBD (18 June 2019) until DLP (17 June 2024), an estimated cumulative total of 4966 patients have received entrectinib from marketing experience, see Annex 7B for further details.

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 (≥25% of patients) include constipation, dysgeusia, fatigue, dizziness, diarrhoea, nausea, dyspnoea, oedema peripheral, and anaemia (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. Entrectinib will also be available as film-coated granules packaged in sachets. Each sachet contains 50 mg entrectinib.

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

- Section 4.2 (Posology and method of administration) in the SmPC covers BSA-based dosing in paediatric patients >6 months and patients >1 month ≤6 months.
- 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 counselling by the health care provider to the legal guardian of the paediatric patient at the time of prescribing. In addition, the PIL advises patients and caregivers that the doctor will calculate the correct dose to use – based on the height and weight of the child, and review and change it as needed.

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 tumours. 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

No risks were reclassified as of this update to the EU RMP.

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 (High Level Group Term [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 remodelling processes (Su et al. 2018). TRKA was noted in animal models to be involved in local bone remodelling (Tomlinson et al. 2017). Inhibition of TRKA signalling reduced the load-induced bone formation in mice. An article describing bone remodelling 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.

A computer-aided modeling experiment of pharmacological targets of entrectinib and an analysis of co-cultures of entrectinib and M5 in a bone cellular matrix were completed to further elucidate potential mechanisms of entrectinib-associated fractures. These studies demonstrated that entrectinib and its metabolite, M5, increased markers of osteoclastogenesis and reduced markers of osteoblastic activity, which is consistent with a possible underlying biologic mechanism in bone maintenance as suggested in the literature.

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).

Additional evidence for paediatric patients is provided in Table 16 from Studies CO40778 (STARTRK-NG), BO41932 (TAPISTRY), and GO40782 (STARTRK-2) through a CCOD of 2 August 2022.

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. The incidence of fracture was 5.3% (n=25/475 [95% CI: 3.43, 7.67) in adults and 20.7% (n=6/29 [95% CI: 7.99, 39.72) in paediatric patients (Table 16). 2.4% (n=12) of 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 ≥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 fracture 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.

Of the 76 patients in the expanded paediatric population as of a CCOD of 2 August 2022, 19 (25.0%) experienced fracture events, of whom 2 patients (2.6%) had Grade 1 events, 9 patients (11.8%) had Grade 2 events, and 8 patients (10.5%) had Grade 3 events. Nine patients (11.8%) had fracture events that were reported as serious, and 4 patients (5.3%) had fractures that were reported as unresolved (Table 17).
Five patients (6.6%) discontinued entrectinib due to fractures.

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. The incidence of fracture was 5.3% (n=25/475 [95% CI: 3.43, 7.67]) in adults and 20.7% (n=6/29 [95% CI: 7.99, 39.72]) in paediatric 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). In the expanded paediatric population of 76 patients (CCOD 2 August 2022), 4 patients (5.3%) experienced fracture events reported as unresolved, and 5 patients (6.6%) discontinued entrectinib due to fractures. 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 labelling is considered sufficient to appropriately inform and mitigate the public health impact of fractures events.

Table 16 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 (N=113)	ROS1 NSCLC-Adult (N=210)	Other-Adult (N=152)	Total-Adult (N=475)	Pediatric (N=29)	Total (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>=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.
AE = adverse event; No. = number; pts = patients; CI = Confidence Interval.
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18OCT2019 12:59 Page 1 of 1

Table 17 Fractures Seriousness, Outcomes, Severity and Frequency with 95% CI (Expanded Paediatric Population)

Seriousness, Outcomes, Severity, Frequency with 95% CI, Bone and Fracture Injuries, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

Fractures

	NTRK - Pediatric (N=39)	ROS1 - Pediatric (N=19)	Other - Pediatric (N=18)	Total - Pediatric (N=76)
Number of Patients with Adverse Events	10 (25.6%)	6 (31.6%)	3 (16.7%)	19 (25.0%)
95% CI for Incidence Rate (Clopper-Pearson)	(13.04, 42.13)	(12.58, 56.55)	(3.58, 41.42)	(15.77, 36.26)
Number of Patients with at least one AE by worst grade				
Grade 1	1 (2.6%)	1 (5.3%)	0	2 (2.6%)
Grade 2	5 (12.8%)	3 (15.8%)	1 (5.6%)	9 (11.8%)
Grade 3	4 (10.3%)	2 (10.5%)	2 (11.1%)	8 (10.5%)
No. of Patients with at least one Serious AE	4 (10.3%)	4 (21.1%)	1 (5.6%)	9 (11.8%)
No. of Patients with at least one AE Unresolved	2 (5.1%)	1 (5.3%)	1 (5.6%)	4 (5.3%)

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 25.
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; CI = Confidence Interval.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

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SVII.3.1.1.2 Congestive Heart Failure

MedDRA terms:

Cardiac failure (SMQ [Standardised MedDRA Query]) - 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).

Additional evidence for paediatric patients is provided in Table 19 from studies CO40778 (STARTRK-NG), BO41932 (TAPISTRY), and GO40782 (STARTRK-2) through a CCOD of 2 August 2022.

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 18). 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 18.

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 upon institution of appropriate clinical management, and/or entrectinib dose interruption/reduction. At the time of the CCOD, 0.6% (n = 3) of patients had at least one event that was unresolved (Table 18).

Of the 76 patients in this expanded paediatric population, 3 patients (3.9%) experienced CHF events, of whom one patient each (1.3%) experienced events reported as Grade 1, Grade 2, or Grade 4. One patient (1.3%) experienced a CHF event that was reported as serious. One patient had an event of CHF that remained unresolved (Table 19).

Monitoring and management of CHF should minimise 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^2, sedentary life style, abnormality in lipid profile, hypertension, diabetes, atrial fibrillation, valvular heart disease, alcohol abuse, infection, and cardiomyopathy of an unknown cause (McMurray and Pfeffer 2005; Chargari et al. 2011; National Clinical Guideline Centre 2018).

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 oedema, 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 institution of appropriate clinical management, the impact of CHF on public health is considered to be low.

Table 18 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 (N=113)	ROS1 NSCLC-Adult (N=210)	Other-Adult (N=152)	Total-Adult (N=475)	Pediatric (N=29)	Total (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.

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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.

Table 19 Congestive Heart Failure: Seriousness, Outcomes, Severity and Frequency with 95% CI (Expanded Paediatric Population)

Seriousness, Outcomes, Severity, Frequency with 95% CI, Congestive Heart Failure, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

Congestive Heart Failure

	NTRK - Pediatric (N=39)	ROS1 - Pediatric (N=19)	Other - Pediatric (N=18)	Total - Pediatric (N=76)
Number of Patients with Adverse Events	2 (5.1%)	1 (5.3%)	0	3 (3.9%)
95% CI for Incidence Rate (Clopper-Pearson)	(0.63, 17.32)	(0.13, 26.03)	(0.00, 18.53)	(0.82, 11.11)
Number of Patients with at least one AE by worst grade				
Grade 1	1 (2.6%)	0	0	1 (1.3%)
Grade 2	0	1 (5.3%)	0	1 (1.3%)
Grade 4	1 (2.6%)	0	0	1 (1.3%)
No. of Patients with at least one Serious AE	1 (2.6%)	0	0	1 (1.3%)
No. of Patients with at least one AE Unresolved	0	1 (5.3%)	0	1 (1.3%)

Investigator text for AEs encoded using MedDRA version 25.
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; CI = Confidence Interval.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

Program: root/clinical_studies/RO7102122/share/pool_aco_2022/prod/program/t_ae_rmp.sas
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09JAN2023 12:00 Page 1 of 1

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 μM) indicate a potential liability for QT prolongation at a 30-fold multiple to unbound human mean $C_{max,ss}$ (0.018 μM). 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 ~0.002 μM (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).

Additional evidence for paediatric patients is provided from studies CO40778 (STARTRK-NG), BO41932 (TAPISTRY), and GO40782 (STARTRK-2) through a CCOD of 2 August 2022 (Table 21).

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 20). Overall, the proportion of patients with QTc interval prolongation AEs was higher in paediatric 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 20). 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).

Of the 76 patients in the expanded paediatric population as of a CCOD of 2 August 2022, 4 (5.3%) experienced QT prolongation events; 2 patients each (2.6%) had Grade 1 and Grade 2 events. None of the QT prolongation events in this population was reported as serious or unresolved (Table 21).

Monitoring, early identification and management of QT prolongation should adequately protect the patient from potential life-threatening outcomes, thereby minimising 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 programme), it is likely to have minimal public health impact.

Table 20 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 (N=113)	ROS1 NSCLC-Adult (N=210)	Other-Adult (N=152)	Total-Adult (N=475)	Pediatric (N=29)	Total (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.

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Table 21 QT Prolongation: Seriousness, Outcomes, Severity and Frequency with 95% CI (Expanded Paediatric Population)

Seriousness, Outcomes, Severity, Frequency with 95% CI, QT Interval Prolongation, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

QT Prolongation

	NTRK - Pediatric (N=39)	ROS1 - Pediatric (N=19)	Other - Pediatric (N=18)	Total - Pediatric (N=76)
Number of Patients with Adverse Events	2 (5.1%)	2 (10.5%)	0	4 (5.3%)
95% CI for Incidence Rate (Clopper-Pearson)	(0.63, 17.32)	(1.30, 33.14)	(0.00, 18.53)	(1.45, 12.93)
Number of Patients with at least one AE by worst grade				
Grade 1	2 (5.1%)	0	0	2 (2.6%)
Grade 2	0	2 (10.5%)	0	2 (2.6%)
No. of Patients with at least one Serious AE	0	0	0	0
No. of Patients with at least one AE Unresolved	0	0	0	0

Investigator text for AEs encoded using MedDRA version 25.
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; CI = Confidence Interval.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

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09JAN2023 12:01 Page 1 of 1

SVII.3.1.2 Information on Important Potential Risks

SVII.3.1.2.1 Severe Neurologic Reactions

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

PTs of altered state of consciousness, amnesia, amnestic 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; ≥ Grade 3), dysesthesias AEs (PTs of paraesthesia, hyperaesthesia, hypoaesthesia, dysaethesia; ≥ Grade 3), Ataxia AEs (PTs ataxia, balance disorder, gait disturbances; ≥ 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; Aboulkassim et al. 2011).

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

involvement in cognition as well as mood-related behaviours (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 in the initial population (n=122 [95% CI: 20.53, 28.19]) experienced at least one cognitive disorder event (Table 22). 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 22).

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%).

In the expanded paediatric population, a total of 11 patients (14.5%) experienced AEs considered as severe neurologic reactions: 8 patients (10.5%) experienced Grade 1 events, 2 patients (2.6%) experienced Grade 2 events, and 1 patient (1.3%) experienced

a Grade 3 event (Table 23). None of the events was considered serious. As of the CCOD of 2 August 2022, 4 patients (5.3%) in this population had at least one event of severe neurologic reaction unresolved.

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) peripheral sensory 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, dysaethesia; 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 [redacted]-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 [redacted] –year old paediatric patient. No Grade 3 or higher events were reported. All patients experiencing seizures had either brain metastases or primary brain tumour 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 programme, 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 counselled 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 22 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 (N=113)	ROS1 NSCLC-Adult (N=210)	Other-Adult (N=152)	Total-Adult (N=475)	Pediatric (N=29)	Total (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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Table 23 Severe Neurological Reactions in Paediatric Patients: Seriousness, Outcomes, Severity and Frequency with 95% CI (Expanded Paediatric Population)

Seriousness, Outcomes, Severity, Frequency with 95% CI, Severe Neurologic Reactions, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

Severe Neurologic Reactions

	NTRK - Pediatric (N=39)	ROS1 - Pediatric (N=19)	Other - Pediatric (N=18)	Total - Pediatric (N=76)
Number of Patients with Adverse Events	5 (12.8%)	1 (5.3%)	5 (27.8%)	11 (14.5%)
95% CI for Incidence Rate (Clopper-Pearson)	(4.30, 27.43)	(0.13, 26.03)	(9.69, 53.48)	(7.45, 24.42)
Number of Patients with at least one AE by worst grade				
Grade 1	2 (5.1%)	1 (5.3%)	5 (27.8%)	8 (10.5%)
Grade 2	2 (5.1%)	0	0	2 (2.6%)
Grade 3	1 (2.6%)	0	0	1 (1.3%)
No. of Patients with at least one Serious AE	0	0	0	0
No. of Patients with at least one AE Unresolved	3 (7.7%)	1 (5.3%)	0	4 (5.3%)

Investigator text for AEs encoded using MedDRA version 25.
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; CI = Confidence Interval.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

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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; Aboulkassim 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 haematological 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 in the initial paediatric population were less than 18 including 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 24). The reported events were aphasia (two events in one patient) and disturbance in attention (one event in one patient).

Both paediatric patients with neuro-developmental impairment in the initial paediatric population 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 26, Table 27, Table 28, Table 29, Table 30, Table 32). Two paediatric patients (6.9%) experienced Cognitive and Attention Disorders and Disturbance of Grade 1 severity and both the events resolved.

In the expanded paediatric population, no patients experienced developmental disorder, developmental disorder cognitive, or intellectual disabilities. A total of 5 patients in this population (6.6%) experienced cognitive and attention disorders and disturbances: 3 patients (3.9%) experienced Grade 1 events and 2 patients (2.6%) experienced Grade 2 events (Table 25).

One patient experienced Grade 2 speech and language abnormalities, which remained unresolved (Table 25). No AEs classed as neurodevelopmental impairment were assessed as serious in this population.

One patient (1.3%) experienced Grade 1 abnormal reflexes, which remained unresolved (Table 31).

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), and GO40782 (STARTRK-2) studies.

Public health impact:

The impact on public health is expected to be minimal.

Table 24 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 (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 25 Neuro-developmental Impairment in Paediatric Patients: Seriousness, Outcomes, Severity and Frequency with 95% CI (Expanded Paediatric Population)

Seriousness, Outcomes, Severity, Frequency with 95% CI, Neuro-developmental Impairment, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

Neuro-developmental Impairment

	NTRK - Pediatric (N=39)	ROS1 - Pediatric (N=19)	Other - Pediatric (N=18)	Total - Pediatric (N=76)
Number of Patients with Adverse Events	4 (10.3%)	1 (5.3%)	1 (5.6%)	6 (7.9%)
95% CI for Incidence Rate (Clopper-Pearson)	(2.87, 24.22)	(0.13, 26.03)	(0.14, 27.29)	(2.95, 16.40)
Number of Patients with at least one AE by worst grade				
Grade 1	2 (5.1%)	1 (5.3%)	1 (5.6%)	4 (5.3%)
Grade 2	2 (5.1%)	0	0	2 (2.6%)
No. of Patients with at least one Serious AE	0	0	0	0
No. of Patients with at least one AE Unresolved	4 (10.3%)	1 (5.3%)	0	5 (6.6%)

Investigator text for AEs encoded using MedDRA version 25.
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; CI = Confidence Interval.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

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Table 26 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 (N=113)	ROS1 NSCLC-Adult (N=210)	Other-Adult (N=152)	Total-Adult (N=475)	Pediatric (N=29)	Total (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]						
Grade 2	0	1 (0.5%)	0	1 (0.2%)	0	1 (0.2%)
Outcomes:						
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 27 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 (N=113)	ROS1 NSCLC-Adult (N=210)	Other-Adult (N=152)	Total-Adult (N=475)	Pediatric (N=29)	Total (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 28 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 (N=113)	ROS1 NSCLC-Adult (N=210)	Other-Adult (N=152)	Total-Adult (N=475)	Pediatric (N=29)	Total (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 29 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 (N=113)	ROS1 NSCLC-Adult (N=210)	Other-Adult (N=152)	Total-Adult (N=475)	Pediatric (N=29)	Total (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 30 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 (N=113)	ROS1 NSCLC-Adult (N=210)	Other-Adult (N=152)	Total-Adult (N=475)	Pediatric (N=29)	Total (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 31 Abnormal Reflexes in patients: Seriousness, Outcomes, Severity and Frequency with 95% CI (Expanded Paediatric Population)

Seriousness, Outcomes, Severity, Frequency with 95% CI, Abnormal Reflexes, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

Abnormal Reflexes

	NTRK - Pediatric (N=39)	ROS1 - Pediatric (N=19)	Other - Pediatric (N=18)	Total - Pediatric (N=76)
Number of Patients with Adverse Events	1 (2.6%)	0	0	1 (1.3%)
95% CI for Incidence Rate (Clopper-Pearson)	(0.06, 13.48)	(0.00, 17.65)	(0.00, 18.53)	(0.03, 7.11)
Number of Patients with at least one AE by worst grade				
Grade 1	1 (2.6%)	0	0	1 (1.3%)
No. of Patients with at least one Serious AE	0	0	0	0
No. of Patients with at least one AE Unresolved	1 (2.6%)	0	0	1 (1.3%)

Investigator text for AEs encoded using MedDRA version 25.
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; CI = Confidence Interval.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

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Table 32 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 (N=113)	ROS1 NSCLC-Adult (N=210)	Other-Adult (N=152)	Total-Adult (N=475)	Pediatric (N=29)	Total (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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Table 33 Speech and Language Abnormalities in Patients: Seriousness, Outcomes, Severity and Frequency with 95% CI (Expanded Paediatric Population)

Seriousness, Outcomes, Severity, Frequency with 95% CI, Speech and Language Abnormalities, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

Speech and Language Abnormalities

	NTRK - Pediatric (N=39)	ROS1 - Pediatric (N=19)	Other - Pediatric (N=18)	Total - Pediatric (N=76)
Number of Patients with Adverse Events	1 (2.6%)	0	0	1 (1.3%)
95% CI for Incidence Rate (Clopper-Pearson)	(0.06, 13.48)	(0.00, 17.65)	(0.00, 18.53)	(0.03, 7.11)
Number of Patients with at least one AE by worst grade				
Grade 2	1 (2.6%)	0	0	1 (1.3%)
No. of Patients with at least one Serious AE	0	0	0	0
No. of Patients with at least one AE Unresolved	1 (2.6%)	0	0	1 (1.3%)

Investigator text for AEs encoded using MedDRA version 25.
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; CI = Confidence Interval.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

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SVII.3.2 Presentation of the Missing Information

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 ≥ 12 months experiencing at least one AE.

Population in need of further characterization:

A limited number of patients have been treated with entrectinib for ≥ 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 34 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Congestive heart failure • QT prolongation • Fractures
Important potential risks	• Severe neurologic reactions • Neuro-developmental impairment in paediatric patients
Missing information	• Safety in long term use

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION 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 for pregnancy and/or breastfeeding: Not applicable.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities and the ongoing post-authorization efficacy studies (PAESs), as described in Table 35 are considered by the Market Authorisation Holder (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

Not applicable.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

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

Table 35 Planned and Ongoing Post-Authorisation Imposed Efficacy Studies

Study Status	Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorisation				
Randomized, open–label, multicentre, 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. **MO41552** Ongoing	In order to further characterize the efficacy of entrectinib in patients with baseline CNS disease, the MAH should conduct and submit the results of a randomized 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
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation				
An open-label, multicentre, global Phase 2 basket study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumours that harbour NTRK1/2/3, ROS1, or ALK gene rearrangements. **RXDX-101-02** **STARTRK-2** **GO40782**	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.	Histology–independent efficacy in adult patients	Interim report (SOB) Final report (SOB)	31 December 2023 31 March 2027

Table 35 Planned and Ongoing Post-Authorisation Imposed Efficacy Studies

Study Status	Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Ongoing	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.			
A phase 1/2, open-label, dose-escalation and expansion study of entrectinib (RXDX-101) in paediatrics with locally advanced or metastatic solid or primary CNS tumours and/or who have no satisfactory treatment options. **RXDX-101-03 STARTRK-NG[1] CO40778** 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. 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.	Histology-independent efficacy in paediatric patients	Interim report (SOB) Final report (SOB)	31 December 2023 31 March 2027

Table 35 Planned and Ongoing Post-Authorisation Imposed Efficacy Studies

Study Status	Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
A Phase 2, global, multicentre, 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 tumours determined to harbour 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. **TAPISTRY BO41932** 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. 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.	Histology-independent efficacy in paediatric and adult patients	Interim report (SOB) Final report (SOB)	31 December 2023 31 March 2027

ALK = anaplastic lymphoma kinase; CNS = central nervous system; MAH = Marketing Authorization Holder; NGS = next generation sequencing; NSCLC = non-small cell lung cancer; NTRK = neurotrophic receptor tyrosine kinase; PFS = progression-free survival; ROS1 = ROS proto-oncogene 1, receptor tyrosine kinase; SOB = specific obligation; TMB = tumour mutational burden.

[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-MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK-MINIMISATION ACTIVITIES)

RISK-MINIMISATION PLAN

V.1 ROUTINE RISK-MINIMISATION MEASURES

Table 36 Description of Routine Risk-Minimisation Measures by Safety Concern

Safety concern	Routine Risk-Minimisation Activities
Fractures	**Routine risk communication:** SmPC Section 4.4 – Special warnings and precautions for use SmPC Section 4.8 – Undesirable effects. **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** Section 4.4 (Fractures) and Section 4.8 (undesirable effects) of the SmPC provide recommendations on risk management approach **Other risk-minimisation measures beyond the Product Information:** None **Medicine's legal status:** Entrectinib is a prescription only medicine
Congestive Heart Failure	**Routine risk communication:** SmPC Section 4.2 – Posology and Method of Administration SmPC Section 4.4 – Special warnings and precautions for use SmPC Section 4.8 – Undesirable Effects **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** 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 **Other risk-minimisation measures beyond the Product Information:** None **Medicine's legal status:** Entrectinib is a prescription only medicine
QT Prolongation	**Routine risk communication:** SmPC Section 4.2 – Posology and Method of Administration SmPC Section 4.4 – Special warnings and precautions for use SmPC Section 4.8 – Undesirable Effects **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** Section 4.2 (Dose modifications), Section 4.4 (QTc Prolongation) and Section 4.8 (undesirable effects) of the

Table 36 Description of Routine Risk-Minimisation Measures by Safety Concern

Safety concern	Routine Risk-Minimisation Activities
	SmPC provide recommendations on risk management approach **Other risk-minimisation measures beyond the Product Information:** None **Medicine's legal status:** Entrectinib is a prescription only medicine
Neuro-developmental impairment in paediatric patients	**Routine risk communication:** SmPC Section 4.2 – Posology and Method of Administration SmPC Section 4.4 – Special warnings and precautions for use SmPC Section 5.3 – Juvenile rat toxicology study **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** 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 **Other risk-minimisation measures beyond the Product Information:** None **Medicine's legal status:** Entrectinib is a prescription only medicine
Severe neurologic reactions	**Routine risk communication:** SmPC Section 4.2 – Posology and Method of Administration SmPC Section 4.4 – Special warnings and precautions for use SmPC Section 4.7 – Effects on ability to drive and use machines **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** 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 **Other risk-minimisation measures beyond the Product Information:** None **Medicine's legal status:** Entrectinib is a prescription only medicine
Safety in long term use	**Routine risk communication:** SmPC Section 4.2 – Posology and Method of Administration (Special Populations) SmPC Section 5.2 – Pharmacokinetic Properties

Table 36 Description of Routine Risk-Minimisation Measures by Safety Concern

Safety concern	Routine Risk-Minimisation Activities
	Routine risk-minimisation activities recommending specific clinical measures to address the risk: Not applicable **Other risk-minimisation measures beyond the Product Information:** None **Medicine's legal status:** Entrectinib is a prescription only medicine

SmPC=Summary of Product Characteristics.

V.2 ADDITIONAL RISK-MINIMISATION MEASURES

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

V.3 SUMMARY OF RISK-MINIMISATION MEASURES

Table 37 Summary Table of Pharmacovigilance Activities and Risk-Minimisation Activities by Safety Concern

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

Table 37 Summary Table of Pharmacovigilance Activities and Risk-Minimisation Activities by Safety Concern

Safety concern	Risk Minimisation Measures	Pharmacovigilance Activities
	animal studies) provide recommendations on risk management approach if neurocognitive changes development. **Additional risk-minimisation measures:** None	**Additional pharmacovigilance activities:** Risk continues to be further assessed as part of PAES CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].
Severe Neurologic Reactions	**Routine risk-minimisation measures:** SmPC Sections 4.2 (Dose modifications), Section 4.4 (Cognitive disorders), Section 4.7 – Effects on ability to drive and use machines **Additional risk-minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].
Safety in Long Term Use	**Routine risk-minimisation measures:** None **Additional risk-minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].

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

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PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

Summary of Risk Management Plan for Rozlytrek® (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 minimised, 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 a cancer medicine that contains the active substance 'entrectinib', and is given by oral administration or by enteral administration (e.g., gastric or nasogastric).

Rozlytrek is used to treat either:

- adults, adolescents, and children with solid tumour cancer in various parts of the body that is caused by a change in a gene called 'neurotrophic tyrosine receptor kinase' (*NTRK*), or
- adults with a type of lung cancer called 'non-small cell lung cancer' (NSCLC) that is caused by a change in a gene called '*ROS1'*

Further information about the evaluation of Rozlytrek benefits can be found in Rozlytrek's 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 MINIMISE OR FURTHER CHARACTERIZE THE RISKS

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

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

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised 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 minimise its risks.

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

In addition to these measures, information about adverse events is collected continuously and regularly analysed, 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 minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of 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	• Congestive heart failure • QT prolongation • Fractures
Important potential risks	• Severe neurologic reactions • Neuro-developmental impairment in paediatric patients
Missing information	• Safety in long term use

II.B Summary of Important Risks

Important Identified Risk: Fractures	
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-minimisation measures	**Routine risk-minimisation measures**: SmPC Section 4.4 (Fractures) and Section 4.8 of the SmPC provide recommendations on risk management approach **Additional risk-minimisation measures**: None
Additional pharmacovigilance activities	Risk of fractures continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].

ALK = anaplastic lymphoma kinase; NTRK = neurotrophic receptor tyrosine kinase; PAES=Post-authorisation efficacy study; ROS1 = ROS proto-oncogene 1, receptor tyrosine kinase; SmPC=Summary of Product Characteristics.

Important Identified Risk: Congestive Heart Failure	
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^2, sedentary life style, abnormality in lipid profile, hypertension, diabetes, atrial fibrillation, valvular heart disease, alcohol abuse, infection, and cardiomyopathy of an unknown cause 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
Risk-minimisation measures	**Routine risk-minimisation measures**: SmPC Sections 4.2 (Dose modifications) and 4.4 (Congestive heart failure) and Section 4.8 (undesirable effects) provide recommendations on risk management approach **Additional risk-minimisation measures**: None
Additional pharmacovigilance activities	Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY]

ALK=anaplastic lymphoma kinase; NTRK=neurotrophic receptor tyrosine kinase; PAES=Post-authorisation efficacy study; ROS1=ROS proto-oncogene 1, receptor tyrosine kinase; SmPC=Summary of Product Characteristics.

Important Identified Risk: QT Prolongation	
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	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. 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.
Risk-minimisation measures	**Routine risk-minimisation measures**: SmPC Sections 4.2 (Dose modifications) and 4.4 (QTc prolongation) and Section 4.8 (undesirable effects) provide recommendations on risk management approach **Additional risk-minimisation measures**: None
Additional pharmacovigilance activities	Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY]

ALK = anaplastic lymphoma kinase; NTRK = neurotrophic receptor tyrosine kinase; PAES=Post authorisation efficacy study; ROS1 = ROS proto-oncogene 1, receptor tyrosine kinase; SmPC=Summary of Product Characteristics..

Important Potential Risk: Severe Neurological Reactions	
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 programme, 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-minimisation measures	**Routine risk-minimisation measures**: 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 **Additional risk-minimisation measures**: None
Additional pharmacovigilance activities	Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].

ALK = anaplastic lymphoma kinase; NTRK = neurotrophic receptor tyrosine kinase; PAES=Post-authorisation efficacy study; ROS1 = ROS proto-oncogene 1, receptor tyrosine kinase; SmPC=Summary of Product Characteristics.

Important Potential Risk: Neuro-developmental impairment in paediatric patients	
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 ≥ 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 ≥ 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-minimisation measures	**Routine risk-minimisation measures:** 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. **Additional risk-minimisation measures:** None
Additional pharmacovigilance activities	Risk continues to be further assessed as part of PAES CO40778 [STARTRK-NG], and BO41932 [TAPISTRY]

AUC = area under the curve; PAES = post-authorisation efficacy study; SmPC = Summary of Product Characteristics.

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

PAES=post-authorisation efficacy study.

II.C Post-Authorisation Development Plan

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

Study Status	Rationale and objectives	Deadline
[ANX] MO41552 Randomized, open-label, multicentre, 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 (CNS) metastases. Ongoing	In order to further characterize the efficacy of entrectinib in patients with baseline CNS disease, the MAH should conduct and submit the results of a randomized 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

MAH = Marketing Authorization Holder; NSCLC = non-small cell lung cancer; PFS = progression-free survival; ROS1 = ROS proto-oncogene 1, receptor tyrosine kinase.

Studies contributing to pooled analysis Status	Rationale and objectives	Deadline
[SOB] GO40782 (STARTRK-2) An open-label, multicentre, global Phase 2 basket study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumours that harbour NTRK1/2/3, ROS1, or ALK gene rearrangements. Ongoing [SOB] CO40778 (STARTRK-NG) A phase 1/2, open-label, dose-escalation and expansion study of entrectinib (RXDX-101) in paediatrics with locally advanced or metastatic solid or primary central nervous system (CNS) tumours and/or who have no satisfactory treatment options. Ongoing [SOB] BO41932 (TAPISTRY) A Phase 2, global, multicentre, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies	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. 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.	31 March 2027

Study Status	Rationale and objectives	Deadline
or immunotherapy as single agents or in rational, specified combinations in patients with unresectable, locally advanced or metastatic solid tumours determined to harbour 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. Ongoing		

ALK=anaplastic lymphoma kinase; MAH=Marketing Authorization Holder; NGS=next generation sequencing; NTRK=neurotrophic receptor tyrosine kinase; ROS1=ROS proto-oncogene 1, receptor tyrosine kinase; SOB=specific obligation; TMB=tumour mutational burden.

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

Not applicable.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6

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

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (If Applicable)

Not applicable