25 April 2024
EMA/246178/2024 Corr.1[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rozlytrek

International non-proprietary name: Entrectinib

Procedure No. EMEA/H/C/004936/X/0017/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] 13 March 2025 : Fig 9 and 11 were amended to correct an error in the calculation of the best percentage change from baseline in tumor size (applicable to measurable/target lesions only) per BICR

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Definition
ALK	anaplastic lymphoma kinase
AR	acceptable range
BE	bioequivalence
CFR	Code of Federal Regulations
CMA	critical material attribute
CPP	critical process parameter
CQA	critical quality attribute
EC	European Commission
HPLC	high-performance liquid chromatography
HPMC	hydroxypropyl methylcellulose
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFU	instruction for use
IPC	in-process control
KF	Karl Fischer titration
MA	material attribute
MCC	microcrystalline cellulose
NG	nasogastric
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
OFAT	one factor at a time
pCMA	potential critical material attribute
pCPP	potential critical process parameter
pCQA	potential critical quality attribute
PE	Polyethylene
PEG	polyethylene glycol
PERA	paediatric excipients risk assessment
PET	polyethylene terephthalate
PET/AL/PE	Polyethylene terephthalate/Aluminium/Polyethylene
PP	process parameter
QbD	quality-by-design
QRA	quality risk assessment
QTPP	quality target product profile
rBA	relative bioavailability
RC	roller compaction
RH	relative humidity
SGFsp	simulated gastric fluid sine pepsin
SmPC	Summary of Product Characteristics
SSF	sodium stearyl fumarate
UDU	uniformity of dosage units
UV	ultraviolet
CLint	Intrinsic clearance
CYP	Cytochrome P450
EC50	50% effective concentration
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HLM	Human liver microsomes
IC50	50% inhibitory concentration
NADPH	Nicotinamide adenine dinucleotide phosphate
PK	Pharmacokinetic(s)
RAF	Relative activity factor
rh	Recombinant human
TDI	Time-dependent inhibition
AE	adverse event
API	active pharmaceutical ingredient
AUC	area under the concentration-time curve
AUCss	area under the concentration-time curve at steady state
AUC0-inf	area under the concentration-time curve to infinite time
BICR	blinded Independent Central Review
BM	brain metastases
BMD	bone mineral density
BMI	body mass index
BP	briefing package

Abbreviation	Definition
BSA	body surface area
CBR	clinical benefit rate
CCOD	clinical cutoff date
CI	confidence interval
Cmax	maximum concentration observed
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
DLT	dose-limiting toxicity
DO2	Division of Oncology 2
DO3	Division of Oncology 3
DOR	duration of response
DXA	dual X-ray absorptiometry
EBE	Empirical Bayesian Estimate
ECOD	enrolment cutoff date
FaSSGF	fasted state simulated gastric fluid
FDA	Food and Drug Administration
GNE	Genentech
HER2	human epidermal growth factor receptor 2
HPMC	hydroxypropyl methylcellulose
IMT	inflammatory myofibroblastic tumour
IND	Investigational New Drug
IRC	Independent Review Committee
MAP	maximum a posteriori
MIBG	metaiodobenzylguanidine
MTD	maximum tolerated dose
NCA	non-compartmental analysis
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NE	not evaluable
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
ODD	orphan drug designation
ORR	objective response rate
OS	overall survival
PBPK	physiologically based PK
PBBM	physiologically based biopharmaceutics modelling
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PMP	pre-meeting package
PMR	Post Marketing Requirement
PopPK	population PK
PR	partial response
PROs	patient-reported outcomes
PT	preferred term
QD	once daily
R/R	relapsed or refractory
RANO	Response Assessment in Neuro-Oncology Criteria
rBA	relative bioavailability
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	recommended Phase 2 dose
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SCE	summary of clinical efficacy
SCP	summary of clinical pharmacology
SCS	summary of clinical safety
SD	stable disease
sNDA	supplemental New Drug Application
SOC	system organ class
Tmax	time to maximum concentration
TMB	tumour mutational burden
TRKA/B/C	tropomyosin receptor kinases A/B/C
TTR	time to response

Abbreviation	Definition
USPI	U.S. Package Insert
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

Roche Registration GmbH submitted on 24 April 2023 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to:
1) Introduce a new pharmaceutical form (coated granules) associated with a new strength (50 mg).
2) Introduce a new route of administration (gastroenteral use) for the already authorised 100 mg and 200 mg hard capsules presentations.

The above two line extensions are grouped with 3 type II variations:
- C.I.6.a - To extend the currently approved indication in solid tumours with NTRK gene fusion to patients from birth to 12 years of age (both for the coated granules and already approved hard capsules presentations).
- C.I.6.a - To add a new paediatric indication from birth to 18 years of age for patients with solid tumours with a ROS1 gene fusion (both for the coated granules and already approved hard capsules presentations). Based on final results from studies CO40778 (STARTRK-NG), GO40782 (STARTRK-2) and BO41932 (TAPISTRY). Study CO40778 is a Phase I/II open-label, dose-escalation and expansion study of entrectinib in paediatrics with locally advanced or metastatic solid or primary CNS tumours and/or who have no satisfactory treatment options; Study GO40782 is an open-label, multicenter, global Phase II basket study of entrectinib for the treatment of patients with solid tumours that harbor an NTRK1/2/3, ROS1, or ALK gene rearrangement (fusion), and Study BO41932 is a Phase II, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in participants with unresectable, locally advanced or metastatic solid tumours determined to harbor specific oncogenic genomic alterations or who are tumour mutational burden (TMB)-high as identified by a validated next-generation sequencing (NGS) assay.
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.3, 6.4 and 6.6 of the SmPC are updated accordingly. The Package Leaflet and Labelling are updated in accordance.
- C.I.4 - To add wording regarding the option of suspension in water of the content of the capsules to be used orally or via the e.g., gastric or nasogastric tube (in sections 4.2 and 5.2 of the SmPC).

The RMP (version 5) is updated in accordance.
The MAH took the opportunity to introduce minor editorial changes to the PI and to update Annex II of the SmPC.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0351/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0351/2021 was completed.

The PDCO issued an opinion on compliance for the PIP P/0351/2021.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The NTRK-fusion positive solid tumour independent indication was discussed overall prior to the initial MAA during the interactions with CHMP within the PRIME scheme. The paediatric requirements were also included in the PIP.

At the initial MAA, Rozlytrek was also approved for adult patients with ROS1-positive, advanced NSCLC not previously treated with ROS1 inhibitors.

Regarding the sought ROS1 positive solid tumour site and histology independent indication in paediatric patients, the MAH did not seek Scientific Advice, and the plan was not discussed in the PIP with the PDCO.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Paolo Gasparini

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Bianca Mulder

The application was received by the EMA on	24 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 August 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	16 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	14 September 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	8 December 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	24 January 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 February 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	22 February 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	21 March 2024
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	22 April 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rozlytrek on	25 April 2024
The CHMP adopted a report on similarity of Rozlytrek with to burosumab, dinutuximab beta, tebentafusp, lutetium (177Lu), avapritinib, cabozantinib, sorafenib tosylate, irinotecan hydrochloride trihydrate, pemigatinib, ripretinib, ivosidenib, niraparib, dabrafenib, trametinib and retifanlimab on (see Appendix on similarity)	25 April 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The current application seeks to extend the current indication for Rozlytrek in patients with solid tumours that have a NTRK gene fusion to include paediatric patients of all ages (currently approved for over 12 years of age, extension requested from birth to <12 years) and seeks a new indication for the treatment of paediatric patients (from birth to 18 years) with solid tumours that have a ROS1 gene fusion. In addition, this application seeks to register a new formulation of entrectinib (coated granules) and, for the already registered capsules, a new method of administration (oral suspension using capsule formulation) and new route of administration (oral syringe or nasogastric/gastric tube use).

The sought indication is:

Neurotrophic tyrosine receptor kinase (NTRK) gene fusion

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that have a 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 (see sections 4.4 and 5.1).*

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.

Rozlytrek as monotherapy is indicated for the treatment of paediatric patients with solid tumours that have a ROS1 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 ROS1 inhibitor*
- *who have no satisfactory treatment options (see sections 4.4 and 5.1).*

2.1.2. Epidemiology

NTRK fusion positive solid tumours in paediatric patients

Neurotrophic tyrosine receptor kinase fusions have been found in multiple tumour types from both adult and paediatric patients that can be grouped into two general categories according to the frequency at which the

fusions are detected: 1) rare cancer types highly enriched for NTRK fusions; and 2) other less rare cancer types in which NTRK fusions are found at much lower frequencies[2].

Paediatric patients with relapsed or refractory (r/r) NTRK fusion-positive solid tumours represent a rare population (FoundationCORE database, Q1 2019 data cut, see table below). The prevalence remains consistent in recently published data from the same but now larger FoundationCORE database, wherein NGS profiling of 295,676 patient samples identified NTRK gene fusions in 889 of those samples (prevalence of 0.30%)[3]. These data are 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])[4], and also specifically for paediatric / adolescent patients (0.44%[5]; 0.49%[6]). Incidence data from the SEER database (April 2022 release, SEER 2021) was used to estimate the number of patients with the specific indications in the US population. The age-adjusted incidence rates by histology were calculated based on cases diagnosed between 2015 - 2019 in the SEER database. The number of new patients diagnosed per year were then estimated with a total US paediatric population of 74,660,000, which is based on the population and demographic data from the National Demographic Analysis Tables, 2020 (see table below).

[2] Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol. 2018;15(12):731-747.
[3] Westphalen CB, Krebs MG, Le Tourneau C, et al. Genomic context of NTRK1/2/3 fusion-positive tumours from a large real-world population. NPJ Precis Oncol. 2021;5(1):69.
[4] Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med. 2017;23:703-713.
[5] Pavlick D, Schrock AB, Malicki D, et al. Identification of NTRK fusions in paediatric mesenchymal tumours. Pediatr Blood Cancer. 2017;64:1-5.
[6] Chmielecki J, Bailey M, He J, et al. Genomic Profiling of a Large Set of Diverse Pediatric Cancers Identifies Known and Novel Mutations across Tumour Spectra. Cancer Res. 2017;77:509-519.

Table 1: Predicted prevalence and incidence of NTRK fusions in patients aged 0-17 years by tumour histology

Tumour Disease Ontology (DO) with an *NTRK* fusion (FoundationCORE®)[a]	Prevalence of *NTRK* fusions in indicated DO (Foundation-CORE®)[a] (%)	DO Sample Size (Foundation-CORE®)[a] (n)	Rate of disease incidence per 100,000 pts (SEER db)[b]	Estimated # new pts per year with Indicated DO (SEER db)[b] (n)	Predicted # new pts with *NTRK* fusion-positive DO per year (SEER db)[b] (n)	Pts with *NTRK* fusion-positive DO in STARTRK-NG (n)	Pts with *NTRK* fusion-positive DO in TAPISTRY (n)
soft tissue fibrosarcoma	51.72	29	0.004	3	2	7	1
thyroid papillary carcinoma	15.38	65	0.004	3	0	-	-
soft tissue primitive neuroectoderm tumour	9.09	11	0.004	3	0	-	-
spine glioma (nos)	9.09	11	0.006	4	0	3	-
soft tissue hemangioma	7.69	13	0.000	0	0	-	-
unknown primary melanoma	6.25	16	0.000	0	0	-	-
unknown primary (nos)	5.61	107	0.043	32	2	-	-
brain dysembryonic neuroepithelial tumour	5.26	19	0.002	1	0	-	-
soft tissue sarcoma (nos)	5.18	193	0.615	459	24	7	-
brain pleomorphic xanthoastrocytoma	5.00	20	0.048	36	2	-	-
soft tissue sarcoma undifferentiated	5.00	20	0.024	18	1	-	-
schwannoma	4.76	21	0.001	1	0	-	-
soft tissue inflammatory myofibroblastic tumour	4.55	44	0.000	0	0	-	-
skin melanoma	3.85	26	0.250	187	7	1	-
brain glioblastoma	2.60	231	0.157	117	3	4	-
soft tissue malignant peripheral nerve sheath tumour	2.22	45	0.046	34	1	-	-

Tumour Disease Ontology (DO) with an *NTRK* fusion (FoundationCORE®)[a]	Prevalence of *NTRK* fusions in indicated DO (Foundation-CORE®)[a] (%)	DO Sample Size (Foundation-CORE®)[a] (n)	Rate of disease incidence per 100,000 pts (SEER db)[b]	Estimated # new pts per year with Indicated DO (SEER db)[b] (n)	Predicted # new pts with *NTRK* fusion-positive DO per year (SEER db)[b] (n)	Pts with *NTRK* fusion-positive DO in STARTRK-NG (n)	Pts with *NTRK* fusion-positive DO in TAPISTRY (n)
brain glioma (nos)	1.45	346	2.017	1506	22	4	-
rhabdomyosarcoma (nos)	0.81	123	0.068	51	0	-	-
brain astrocytoma	0.75	133	0.161	120	1	1	-
brain astrocytoma pilocytic	0.64	314	0.763	570	4	-	1
brain medulloblastoma	0.43	233	0.295	220	1	1	-
bone osteosarcoma	0.28	353	0.539	402	1	-	-

db = database; DO = disease ontology; FMI = Foundation Medicine, Inc.; n = number; nos = not otherwise specified; pts = patients; SEER = Surveillance, Epidemiology, and End Results.

Note: There were no paediatric patients in STARTRK-02 whose tumours harboured an *NTRK* fusion.

[a] Predicted prevalence data are from a Q4-2022 cut of the FoundationCORE® commercial testing database at FMI. DOs with fewer than 10 samples were omitted for this analysis. DOs were not shown if not observed in the FoundationCORE® database to harbour an *NTRK* fusion (i.e., 0% prevalence).

[b] DOs harbouring an *NTRK* fusion in the FoundationCORE® database were matched against SEER ICD-O3 codes for biomarker-positive incidence calculations. Incidence-SEER Research Limited Field Data, 22 Registries, Nov 2021 Sub (2000-2019) was used as the source SEER registry. The number of patients with an *NTRK* fusion-positive tumour was estimated with a total US paediatric population of 74,660,000, which is based on the population and demographic data from the National Demographic Analysis Tables, 2020.

ROS1 fusion positive solid tumours in paediatric patients

A summary of the expected prevalence and incidence for observing ROS1 fusion positive tumours by tumour histology, including a comparison to the distribution of tumour types enrolled in the STARTRK-NG, TAPISTRY, and STARTRK-02 studies is presented in the table below. Overall, ROS1 fusion-positive tumours in paediatric patients are extremely rare, but the tumour types enrolled across the three studies were generally consistent with the predicted number of patients, according to the SEER database, with the exception of low-grade glioma, as those being generally highly treatable and curable with current therapies, the Applicant did not expect to enrol them into clinical trial. Based on NGS profiling data of tumour samples from paediatric patients using the Foundation Medicine Inc. platform, ROS1 fusions were estimated to be prevalent in approximately 0.5% solid tumours overall (FoundationCORE database, Q1 2019 data cut).

Table 2: Predicted prevalence and incidence of ROS1 fusions in patients aged 0-17 years by tumour histology

Tumour Disease Ontology (DO) with an *ROS1* fusion (FoundationCORE®)[7]	Prevalence of *ROS1* fusions in indicated DO (Foundation-CORE®)[7] (%)	DO Sample Size (Foundation-CORE®)[7] (n)	Rate of disease incidence per 100,000 pts (SEER db)[8]	Estimated # new pts per year with Indicated DO (SEER db)[8] (n)	Predicted # new pts with *ROS1* fusion-positive DO per year (SEER db)[8] (n)	Pts with *ROS1* fusion-positive DO in STARTRK-NG[9] (n)	Pts with ROS1 fusion-positive DO in STARTRK-29 (n)	Pts with *NTRK* fusion-positive DO in TAPISTRY[9] (n)
soft tissue inflammatory myofibroblastic tumour	20.45	44	0	0	0	6	-	-
soft tissue lymphangioma	7.69	13	0	0	0	-	-	-
soft tissue angiosarcoma	7.14	14	0.004	3	0	-	-	-
soft tissue sarcoma undifferentiated	5.00	20	0.024	18	1	-	-	-
brain embryonal tumour	2.56	39	0.004	3	0	-	-	-
brain anaplastic astrocytoma	2.27	88	0.064	48	1	1	-	-
brain glioma (nos)	1.73	346	2.017	1506	26	1	-	-
brain astrocytoma	1.50	133	0.161	120.203	2	1	-	-
brain astrocytoma pilocytic	0.96	314	0.763	569.656	5	1	-	-
brain glioblastoma (gbm)	0.87	231	0.157	117	1	-	-	1

[7] Predicted prevalence data are from a Q4-2022 cut of the FoundationCore commercial testing database at Foundation Medicine, Inc. Disease ontologies with fewer than 10 samples were omitted for this analysis. Disease ontologies were not shown if not observed in the FoundationCore database to harbour a ROS1 fusion (i.e. 0% prevalence).
[8] Disease ontologies harbouring a ROS1 fusion in the FoundationCore database were matched against SEER ICD-O3 codes for biomarker-positive incidence calculations. Incidence-SEER Research Limited Field Data, 22 Registries, Nov 2021 Sub (2000-2019) was used as the source SEER registry. The number of patients with ROS1 fusion was estimated with a total US paediatric population of 74,660,000, which is based on the population and demographic data from the National Demographic Analysis Tables: 2020 (Middle) https://www.census.gov/data/tables/2020/demo/popest/2020-demographic-analysis-tables.html]
[9] See also more complete frequency breakdown of disease ontologies (histologies) with indicated ROS1 fusion enrolled to STARTRK-NG, STARTRK-2, or TAPISTRY studies

Tumour Disease Ontology (DO) with an *ROS1* fusion (FoundationCORE®)[7]	Prevalence of *ROS1* fusions in indicated DO (Foundation-CORE®)[7] (%)	DO Sample Size (Foundation-CORE®)[7] (n)	Rate of disease incidence per 100,000 pts (SEER db)[8]	Estimated # new pts per year with Indicated DO (SEER db)[8] (n)	Predicted # new pts with *ROS1* fusion-positive DO per year (SEER db)[8] (n)	Pts with *ROS1* fusion-positive DO in STARTRK-NG[9] (n)	Pts with ROS1 fusion-positive DO in STARTRK-29 (n)	Pts with *NTRK* fusion-positive DO in TAPISTRY[9] (n)
brain ependymoma	0.69	145	0.002	2	0	-	-	-
soft tissue sarcoma (nos)	0.52	193	0.615	459	2	3	-	-
non-small cell lung cancer	-	-	-	-	-	-	1	-
glioneuronal	-	-	-	-	-	-	1	-

2.1.3. Biological features

NTRK fusion positive solid tumours in paediatric patients

The neurotrophic receptor tyrosine kinase family of genes NTRK1, NTRK2, and NTRK3 encode the proteins TRKA, TRKB, and TRKC, respectively. Binding of neurotrophins to their cognate TRK receptors results in homodimerization, receptor autophosphorylation and activation of downstream signal transduction pathways involved in cell proliferation, apoptosis, and survival of neurons and other cell types. NTRK gene fusions arise from intra- or inter-chromosomal rearrangements that juxtapose 3' NTRK gene sequences encoding the catalytic tyrosine kinase domain in-frame with various 5' partner gene sequences. The transcribed chimeric TRK proteins have been shown to be oncogenic, promoting tumorigenesis by constitutive ligand-independent kinase activation leading to tumour cell proliferation, differentiation, and/or evasion of apoptosis[10].

ROS1 fusion positive solid tumours in paediatric patients

ROS1 is a proto-oncogene that encodes the tyrosine kinase receptor ROS1 belonging to the insulin receptor family, mainly expressed in the epithelial cells but also found in other tissues. ROS1 can activate signalling pathways correlated with cell differentiation, proliferation, growth and survival[11]. Little is known about wild-type ROS1, and its first ligand neural epidermal growth factor-like 2 (NELL2) was identified only in 2020[12]. ROS1 was discovered in samples from patients with NSCLC in the form of a fusion protein and it is found in approximately 1-2% of NSCLCs[13] [14]. ROS1 gene rearrangements have then been detected in a variety of other cancers, including glioblastoma multiforme (GBM), cholangiocarcinoma, ovarian cancer, gastric adenocarcinoma, colorectal cancer (CRC), inflammatory myofibroblastic tumour (IMT), angiosarcoma, and

[10] Kheder ES, Hong DS. Emerging Targeted Therapy for Tumors with NTRK Fusion Proteins. Clin Cancer Res. 2018 Dec 1;24(23):5807-5814.
[11] Acquaviva, J; Wong, R; Charest, A. The multifaceted roles of the receptor tyrosine kinase ROS in development and cancer. Biochim. Biophys. Acta 2009, 1795, 37–52.
[12] Kiyozumi, D; Noda, T; Yamaguchi, R; Tobita, T; Matsumura, T; Shimada, K; Kodani, M; Kohda, T; Fujihara, T; Ozawa, M; et al. NELL2-mediated lumicrine signalling through OVCH2 is required for male fertility. Science 2020; 368:1132–1135.
[13] Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol. 2012;30:863-70.
[14] Davies KD, Le AT, Theodoro MF, et al. Identifying and targeting ROS1 gene fusions in non-small cell lung cancer. Clin Cancer Res. 2012;18:4570-9.

epithelioid hemangioendothelioma[15] [16]. In paediatric patients, ROS1 gene fusions have been identified in several tumour types, including IMT[17], spitzoid neoplasms[18] and glial tumours[19] [20].

2.1.4. Clinical presentation, diagnosis, stage/prognosis

NTRK fusion positive solid tumours in paediatric patients

With regard to children, NTRK fusions have been described in several tumours in the paediatric age. ETV6-NTRK3 fusion is a characteristic feature of infantile fibrosarcoma as well as in congenital mesoblastic nephroma. NTRK fusion have also been observed with high frequency (i.e. about 40%) in high grade glioma in children[1]. Details on single tumour type have been discussed in the EPAR (see Rozlytrek EPAR).

ROS1 fusion positive solid tumours in paediatric patients

Paediatric patients with relapsed/refractory/advanced/metastatic solid tumours, in general, have poor outcomes, estimating a 10-year PFS and OS of approximately 18% and 25%, respectively[21]. Patients with r/r ROS1 fusion-positive solid tumours represent a rare population (FoundationCORE database, Q1 2019 data cut),

Some additional information (retrieved by the Assessor) regarding single tumours types with identified ROS1 gene fusion are provided below:

Inflammatory myofibroblastic tumour (IMT): IMT is a rare mesenchymal tumour of intermediate malignant potential characterized by spindle-cell proliferation within an inflammatory infiltrate, predominantly affecting children, adolescents and young adults, with median age at diagnosis 9 years of age. IMT can affect any part of the body, most commonly in lung, abdomen, pelvis, and retroperitoneum, and presenting symptoms vary based on primary site, and systemic signs/symptoms may also occur. IMT is typically localized, while multifocal or metastatic disease is uncommon. More than half of IMT carries an ALK gene fusion. Other rearrangements have been identified in ALK negative IMTs, including ROS1, PDGFRβ, RET, NTRK and IGF1R. ROS1 gene fusions have been reported in 6-18% of paediatric and adults IMT (about 20% of ALK-negative IMT)[22] [23]. It is unclear whether non-ALK-positive IMT have different prognosis as compared to ALK-positive IMT[14].

It is reported an overall favourable prognosis for IMT, even for unresectable disease[24]. Complete surgical resection is the treatment of choice when feasible. Local recurrence may occur, and a second surgical

[15] Davies KD, Doebele RC. Molecular pathways: ROS1 fusion proteins in cancer. Clin Cancer Res. 2013;19:4040-5.
[16] Shaw AT, Hsu PP, Awad MM, et al. Tyrosine kinase gene rearrangements in epithelial malignancies. Nature Reviews. Cancer 2013:13:772-87.
[17] Lovly CM, Gupta A, Lipson D, et al. Inflammatory myofibroblastic tumours harbour multiple potentially actionable kinase fusions. Cancer Discov. 2014; 4(8): 889- 895.
[18] Donati M, Kastnerova L, Martinek P, et al. Spitz Tumors With ROS1 Fusions: A Clinicopathological Study of 6 Cases, Including FISH for Chromosomal Copy Number Alterations and Mutation Analysis Using Next-Generation Sequencing. Am J Dermatopathol. 2020 Feb;42(2):92-102.
[19] Clark M, Mackay A, Ismer B, et al. Infant high-grade gliomas comprise multiple subgroups characterized by novel targetable gene fusions and favorable outcomes. Cancer Discov 2020;10:942–63.
[20] Guerreiro Stucklin AS, Ryall S, Fukuoka K, et al. Alterations in ALK/ROS1/NTRK/MET drive a group of infantile hemispheric gliomas. Nat Commun. 2019 Sep 25;10(1):4343.
[21] Cho HW, Lee JW, Ma Y, et al. Treatment outcomes in children and adolescents with relapsed or progressed solid tumours: a 20-year, single-center study. J Korean Med Sci. 2018;33:e260.
[22] Mahajan P, Casanova M, Ferrari A, Fordham A, Trahair T, Venkatramani R. Inflammatory myofibroblastic tumour: molecular landscape, targeted therapeutics, and remaining challenges. Curr Probl Cancer. 2021 Aug;45(4):100768.
[23] Yamamoto H, Yoshida A, Taguchi K, et al. ALK, ROS1 and NTRK3 gene rearrangements in inflammatory myofibroblastic tumours. Histopathology. 2016;69(1):72-83.
[24] Casanova M, Brennan B, Alaggio R, et al. Inflammatory myofibroblastic tumour: the experience of the European paediatric Soft Tissue Sarcoma Study Group (EpSSG) Eur J Cancer, 127 (2020), pp. 123-129.

resection can be considered. Due to the inflammatory nature of IMT, anti-inflammatory agents such as steroids and nonsteroidal anti-inflammatory drugs (NSAIDs) have been used. Chemotherapy can be used in the neoadjuvant setting to allow for surgery, and in the advanced settings, using regimens including drugs like ifosfamide, vincristine, vinblastine, vinorelbine, dactinomycin, cyclophosphamide, doxorubicin, methotrexate[14]. In October 2022, crizotinib was approved in the EU for the treatment of paediatric patients (age ≥6 to < 18 years) with relapsed or refractory ALK-positive unresectable IMT (approved from 1 years of age and including adults in US)[25]. There are no targeted drugs currently approved for non-ALK positive IMT, including ROS1-positive.

Spitzoid neoplasms: Spitz tumours represent a heterogeneous group of melanocytic neoplasms with a spectrum of biological behaviour ranging from benign (Spitz nevus) to malignant (spitzoid melanoma). Those are biologically distinct from conventional melanocytic naevi and melanoma, and mutually exclusive activating kinase fusions, involving ALK, NTRK1, NTRK3, RET, MET, ROS1, and BRAF, have been identified in a subset of spitzoid lesions[26]. Spitzoid tumours commonly arise in children and adolescents, but may occur also in older individuals[15] [27]. Few epidemiological data are available in literature, as these lesions are rare, with only 1-2% of all melanocytic lesions in all ages[28]. ROS1 fusions are seen in up to 10% of Spitz tumours[23]. Spitz tumours with ROS1 fusions have common histopathological characteristics, but no specific cytological and histological features are associated with ROS1 fusion. Currently, SM is typically managed using the same guidelines as conventional melanoma, however, Spitz melanoma may not require the same aggressive treatment protocol[24] [29].

Glioma: Data on ROS1 fusions in glioma are mostly limited to individual case reports or small case series, with an enrichment of approximately 7% of ROS1 fusions identified in gliomas within the paediatric population[30] [31]. Gliomas are the most common primary CNS tumours and result in the highest tumour-associated morbidity and mortality in children and adults. Traditionally, gliomas are divided into low grade (LGG, WHO grades I–II) and high grade (HGG, WHO grades III–IV) based on their histological characteristics. Most childhood LGG are driven by RAS/MAPK activation (most common BRAF mutation) and rarely undergo malignant transformation, while paediatric HGG are usually not the result of transformation from LGG and most commonly harbour recurrent mutations in the genes encoding histones. Less is known about the infant (under 1 year of age), despite the incidence of CNS tumours is highest in this group, and the association between tumour grade and outcome is less predictable as compared to older children[16] [27]. Among infant gliomas, one group has been identified arising in the cerebral hemispheres and harbouring alterations in the receptor tyrosine kinases ALK, ROS1, NTRK and MET, enriched for HGG[28]. Kinase fusion–positive tumours have better outcome and may respond to targeted therapy clinically[16].

[25] EPAR Xalkori II/72, EMA/846028/2022; https://www.ema.europa.eu/en/documents/variation-report/xalkori-h-c-002489-ii-0072-epar-assessment-report-variation_en.pdf
[26] Donati M, Kastnerova L, Martinek P, et al. Spitz Tumors With ROS1 Fusions: A Clinicopathological Study of 6 Cases, Including FISH for Chromosomal Copy Number Alterations and Mutation Analysis Using Next-Generation Sequencing. Am J Dermatopathol. 2020 Feb;42(2):92-102.
[27] Wiesner T, Kutzner H, Cerroni L, Mihm MC Jr, Busam KJ, Murali R. Genomic aberrations in spitzoid melanocytic tumours and their implications for diagnosis, prognosis and therapy. Pathology. 2016 Feb;48(2):113-31.
[28] Cheng TW, Ahern MC, Giubellino A. The Spectrum of Spitz Melanocytic Lesions: From Morphologic Diagnosis to Molecular Classification. Front Oncol. 2022 Jun 7;12:889223.
[29] Batra S. Spitzoid Melanoma of Childhood: A Case Series and Review. Melanoma Manage (2015) 2(2):121–5.
[30] Clarke M, Mackay A, Ismer B, et al. Infant High-Grade Gliomas Comprise Multiple Subgroups Characterized by Novel Targetable Gene Fusions and Favorable Outcomes. Cancer Discov. 2020 Jul;10(7):942-963.
[31] Guerreiro Stucklin AS, Ryall S, Fukuoka K, et al. Alterations in ALK/ROS1/NTRK/MET drive a group of infantile hemispheric gliomas. Nat Commun. 2019 Sep 25;10(1):4343.

2.1.5. Management

NTRK fusion positive solid tumours in paediatric patients

Another TRK inhibitor, larotrectinib (Vitrakvi), is approved in EU under CMA for treatment of adult and paediatric patients with NTRK fusion-positive tumours who have locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options. Larotrectinib indication covers also paediatric patients of all ages. In the paediatric sub-population (n=94), the ORR for Vitrakvi was 84%. An oral solution of Vitrakvi is available for patients who cannot swallow the capsules[32].

ROS1 fusion positive solid tumours in paediatric patients

Patients with r/r ROS1 fusion-positive solid tumours have no currently approved targeted therapies available, but targeted therapy may offer greater efficacy with lesser toxicity relative to traditional cytotoxic chemotherapy, including CNS active treatment for CNS tumours.

2.2. About the product

Entrectinib is an inhibitor of the tropomyosin receptor tyrosine kinases TRKA, TRKB and TRKC (encoded by the neurotrophic tyrosine receptor kinase [NTRK] genes NTRK1, NTRK2 and NTRK3, respectively), proto oncogene tyrosine protein kinase ROS (ROS1), and anaplastic lymphoma kinase (ALK), with IC50 values of 0.1 to 2 nM. The major active metabolite of entrectinib, M5, showed similar in vitro potency and activity against TRK, ROS1, and ALK.

Entrectinib is an antineoplastic agent, of the class of protein kinase inhibitors (ATC code: L01EX14).

The available pharmaceutical form is hard capsule of 100 mg and 200 mg strengths, which should be swallowed whole.

The approved indication is:

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 *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 (see sections 4.4 and 5.1).

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.

[32] Summary of Product Characteristics – Vitrakvi https://www.ema.europa.eu/en/documents/product-information/vitrakvi-epar-product-information_en.pdf accessed July 2023

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as film-coated granules containing 50 mg of entrectinib as active substance in a sachet.

Other ingredients are:

Granule core: microcrystalline cellulose (E460), tartaric acid (E334), silica, colloidal anhydrous (E551), croscarmellose sodium (E468), sodium stearyl fumarate, mannitol (E421) & magnesium stearate (E470b).

Film-coating: titanium dioxide (E171), talc, yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172), polyethylene glycol 3350 & polyvinyl alcohol (partially hydrolysed).

The product is available in a PET/AL/PE laminated foil sachet as described in section 6.5 of the SmPC.

2.3.2. Active Substance

The active substance documentation is identical to that previously approved for the authorised capsule pharmaceutical forms and is acceptable. No new information has been provided.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product is film-coated granules of brownish orange or greyish orange in colour, approximately 2 mm in diameter, the granules are contained in a sachet.

The finished product was developed as a new pharmaceutical form (film-coated granules in a sachet) to enable an extension of indication into further paediatric populations. The granule formulation is intended for those patients who may have difficulty swallowing the capsule formulations but who can swallow soft food and for whom the 50 mg unit dose posology would be suitable. The granules formed are uniform and similar in nature to mini-tablets, they are intended to be swallowed whole and not to be chewed, this is captured in the product information. There are 20 of these coated granules in each sachet and the contents of each sachet are intended as one unit dose.

The manufacture and control of the active substance remains the same as the authorised capsule presentations. The active substance is poorly water soluble and it exhibits polymorphism. The active substance is present as polymorphic form C. The information from the development of the capsule formulation suggests the particle size of the active substance does not impact the in-vivo performance. A control for the particle size is nevertheless included in the active substance specification.

All excipients are well known pharmaceutical ingredients, with the exception of the in-house film-coating mixture. For the compendial excipients their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. Tartaric acid was identified as a key component of the formulation to modify local pH values and impact the dissolution and bioavailability. The level of tartaric acid

was selected in line with the conducted bioequivalence study. The list of excipients is included in section 6.1 of the SmPC, and the suitability in the intended paediatric population was accepted.

The formulation for the granules was initially selected using polymorphic form A of the active substance. This is similar to the approach that was taken for the capsules formulation. During manufacture and development it became apparent that polymorphic form C would be used for the commercial phase of both the approved capsules and the proposed granule formulation. The applicant therefore justified a bridging strategy for the acceptability of polymorphic form C in the granules. This built upon the justification provided already as part of the authorisation for the capsule formulation. During authorisation of the capsules the applicant demonstrated that capsules with polymorphic form A were equivalent to form C through the conduct of a bioequivalence study. Following on from this, the bridge between granules containing polymorphic form A and those containing polymorphic form C was also accepted. In-vitro dissolution studies at three different physiological pH values and using the proposed QC dissolution method were conducted, and comparable dissolution profiles were shown between the granules containing polymorphic form A & C.

The manufacturing process was developed considering the knowledge gained during the development of the capsule formulation. A conventional process was selected involving blending, roller compaction, compression and film-coating. The process was maintained throughout the development programme with minor amendments to improve robustness and accommodate scale and equipment needs. Critical process parameters were identified during development for the film-coating step, with the potential to impact uniformity and appearance identified. This information was used to inform the parameters of the commercial process.

The dissolution method used for quality control was also developed considering the knowledge gained during development of the capsule formulation. The discriminatory potential of the dissolution method has been suitably demonstrated, and the level of the surfactant justified.

The primary packaging is a PET/AL/PE laminated foil sachet. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Suspension prepared from capsule formulation:

The extension application includes grouped variations with Quality aspects, the submission also proposes that the authorised capsule formulations can be used to generate an ad-hoc suspension that can be used to treat some of the proposed paediatric population, including those who cannot swallow the capsules, cannot take the dose by way of the granules, or who may require enteral feeding tube administration.

The suspension is prepared by emptying one or more capsules into an empty cup, and the relevant volume of water or milk is then added. The suspension is allowed to sit for 15 minutes, and is then swirled before administration. Detailed information is included in the product information. Bioequivalence information was gathered between the capsule formulations and the prepared ad-hoc suspensions, for more information please refer to the clinical sections of the report.

The excipients within the capsules and intended for the preparation for the suspension are considered suitable and justified in line with the intended paediatric population. The prepared suspension was found to be suitably compatible with various feeding tubes and oral dosing syringes. The information on administration of the suspension via feeding tubes is outlined in the product information, including relevant flush volumes and minimum tube diameter to prevent clogging of the tube.

Information regarding the uniformity and dose accuracy of the generated suspension was provided and considered acceptable. Upon sedimentation the suspension can be easily redispersed, and the prepared suspension is suitably homogenous and stable when prepared in line with the instructions for use. The prepared ad-hoc suspension should be administered within 2 hours in line with the information from the clinical studies.

2.3.3.2. Manufacture of the product and process controls

The manufacturing process is performed at one finished product manufacture:

The manufacturing process of the granule formulation consists of six main steps: blending, roller compaction & granulation, blending, compression, film-coating and packaging. In the first blending steps the active substance and various excipients are blended, this blend then undergoes roller compaction to generate a granulate. Various extragranular excipients are added with additional blending steps. The granules are then compressed, film-coated and finally packaged into the sachets. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on three commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.3.3.3. Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form; appearance (visual), identification (HPLC & UV), assay (HPLC), uniformity of dosage units (Ph. Eur), degradation products (HPLC), water content (KF), dissolution (HPLC), and microbiological quality (Ph. Eur.).

Limits for degradation products have been set in line with ICH Q3B requirements, and no degradation products are present above the identification threshold.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Additional supportive batch analysis was also provided for certain clinical scale batches that were manufactured at a scale larger than the proposed commercial batch size.

2.3.3.4. Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 18 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. In addition 24 months of long term data and 6 months of accelerated data is available from supportive stability batches stored under the same conditions. The supportive stability batches were manufactured of the same scale, and the only difference is that the supportive stability batches were not tested for microbiological quality parameters.

In addition, one batches was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not considered sensitive to light.

Samples were tested for appearance, assay (HPLC), degradation products (HPLC), water content (KF), dissolution (HPLC), and microbiological quality (Ph. Eur.). The analytical procedures used are stability indicating. No significant changes or degradation of the active substance was observed during the stability testing, however at the accelerated conditions a trend towards decreasing dissolution was observed. Considering this trend an instruction not to store above 30˚C is appropriate.

The granules are hygroscopic, this is linked to the presence of tartaric acid and microcrystalline cellulose in the formulation. For this reason they should be protected from moisture by storing in the original packaging.

With respect to ongoing stability studies, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Based on available stability data, the proposed shelf-life of 24 months and do not store above 30°C. Store in the original package in order to protect from moisture, as stated in the SmPC (section 6.3) are acceptable.

2.3.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.3.4. Discussion on chemical and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The active substance synthesis is the same as for the already approved capsule presentation. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure no major objections were raised on Quality aspects and the relevant other concerns identified were sufficiently resolved by the responses by the applicant.

2.3.5. Conclusions on the chemical and pharmaceutical aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendation(s) for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

2.4.2. Pharmacology

From a non-clinical point of view the data from pharmacology, pharmacokinetics (PK), and toxicology studies conducted for entrectinib were reviewed during the initial marketing application (EMEA/H/C/004936/0000 – see EPAR) and a subsequent variation (EMEA/H/C/004936/II/0010). In the current procedure, new nonclinical information from the following studies were submitted:

Pharmacology

- Entrectinib: HotSpot kinase profiling
- In vitro secondary pharmacology of entrectinib and the M5 metabolite

2.4.2.1. Primary pharmacodynamic studies

Subsequent addenda have been submitted with this application for the extension of the MA for Rozlytrek incorporating new non-clinical information. A further biochemical kinase inhibition profile assessment was performed to evaluate the inhibition potency of entrectinib and M5 against 11 kinases, including anti-target kinases (TXK, MUSK, JAK2, FMS, TYK1/LTK, ACK1, and ITK). Results from the study demonstrated that in the case of entrectinib, the IC50 values for anti-target kinases varied from 0.51 to 104 nM, indicating a range of potencies.

2.4.2.2. Secondary pharmacodynamic studies

In the context of secondary pharmacodynamics, a new study was conducted to measure the interaction of entrectinib and its metabolite M5 at a concentration of 1 μM for those targets that showed ≥ 50% inhibition at 10 μM in study reports submitted with the initial MAA. In addition, some targets that were not assessed previously (5HT1A, NicACh, VMAT2) were included in the analysis. Among the observed IC50 values, the lowest was recorded for Cav1.2 at 1.83 μM. It is worth noting that in humans, the free Cmax,ss (steady-state maximum concentration) for entrectinib is approximately 0.007 μM, while for metabolite M5, it is approximately 0.004 μM.

2.4.2.3. Safety pharmacology programme

No new non-clinical safety pharmacology data have been submitted by the Applicant with this application.

2.4.3. Pharmacokinetics

The pharmacokinetics data of entrectinib, provided with the initial marketing authorization (MA), showed for the product high protein binding in plasma and the ability to effectively cross the blood-brain barrier. This was demonstrated by observing brain-to-plasma concentration ratios in multiple species. These findings are consistent with the observed anti-tumour activity of entrectinib in different intracranial tumour models.

Additional follow-up PK studies were submitted with this application for the two MA extensions for Rozlytrek.

Regarding the distribution of entrectinib a follow-up study was submitted, in order to confirm the previous findings regarding plasma, brain and tumour PK data from the same KM12-Luciferase subcutaneous tumour mouse model used in the original Study Report. At the time of the MA submission, only the plasma concentration data were available with this initial study. The brain and tumour concentration results were intended to be included in the PK Phase Report through a subsequent amendment at a later time. In this follow-up study, these missing values have been provided but only for the 5 mg/kg BID dose regimen At 5 mg/kg approximately half the clinical AUC0-24h of entrectinib at a dose of 250 mg (12.8 μM*h), is reached.

The new data show that both entrectinib and its active metabolite M5 have the highest concentrations in the tumour tissue (with the AUC of M5 being 2.5-fold higher than the AUC of entrectinib) and show a dose-dependent PK/PD relationship in the TRK-dependent tumour model (TPM3-NTRK1) growing subcutaneously. These findings in the tumour matrix together with the previous data on plasma concentrations (confirmed in this follow-up study), support the initial proof of concept of entrectinib in targeting the tumour and exerting its therapeutic effects.

Both entrectinib and M5 show a lower distribution in the CNS as compared to plasma and tumour matrices., the following observations are made:

- Brain levels of M5 are close to those of entrectinib (AUC ratio M5/entrectinib 60%)

- Brain-to-plasma concentration ratios (AUC0-24) of 0.1 and 0.6 for entrectinib and M5, respectively, suggest a higher brain-targeting ability of M5 despite the fact that M5 is a P-gp substrate (whereas entrectinib is a weak P-gp substrate based on in vitro data (see SmPC section 5.2)).

The ability of entrectinib to cross BBB in orally administered mice, confirms the previous finding (see SmPC Section 5.2 - Distribution: "Entrectinib demonstrated steady-state brain-to-plasma concentration ratios of 0.4 to 2.2 in multiple animal species (mice, rats, and dogs) at clinically relevant systemic exposures."). Thus, this non-clinical evidence supports the potential clinical use in patients with locally advanced or metastatic solid or primary CNS tumours subjects of the current procedure (pivotal clinical trial STARTRK-NG).

New in vitro PK studies in human liver microsomes show that:

-similarly to entrectinib, M5 is metabolized mainly by CYP3A isoforms and especially CYP3A4

-CYP3A4 is the main CYP3A isoform involved in the metabolism of entrectinib and M5 in adults but no conclusion can be made on their metabolism in paediatric subjects since only one paediatric liver microsomes donor was included in the study.

-Ketoconazole is the most effective inhibitor of CYP3A4/5, confirming what already known from clinical trials (see SmPC section 4.5).

- entrectinib is expected to be a very weak time dependant inhibitor on CYP3A4.

2.4.4. Toxicology

2.4.4.1. Other toxicity studies

A full set of toxicology studies is available for entrectinib, and these data have been presented and reviewed in the initial MAA. This application includes only new information from the following studies:

- Effect of entrectinib on bone metabolism in vitro (Study Report 1121182)

- RO7288587: Bacterial reverse mutation assay (Study Report 1104576)

Relevant data supporting the paediatric extension application are provided by study 1121182.

An in vitro non GLP study (Study Report 1121182) was carried out in order to investigate entrectinib as well as its main metabolite M5 effects on osteoblast + osteoclast co-cultures representing human juvenile or adult bone models. This study was conducted due to the bone fractures reported in patients less than 12 years of age. Hence, a direct role of entrectinib on bone fracture risk cannot be excluded due to the impact on physiological bone remodelling processes. Moreover, developmental foetal and bone findings were seen both in reprotoxicity and juvenile Toxicity studies. Concentrations of entrectinib and M5 up to 100 nM (lower than the clinical Cmax – 1053 nM and 2075 nM (capsules) and 2032 nM and 836 (coated granules, all paediatric ages) for entrectinib and M5 respectively, were found to dose-dependently decrease osteoblast function and stimulate osteoclastogenesis in all 3 co-cultures, suggesting that the effect on the juvenile bone does not differ from that on the adult one. Overall, the effect on osteoblast function was less pronounced than that on osteoclast function.

Alkaline phosphatase activity and formation of mineralized matrix tended to be decreased by entrectinib or M5 treatment in all three co-culture models, while other osteoblastic markers such as osteocalcin or procollagen type I N-propeptide were not significantly affected or were even slightly increased.

Co-stimulation with the vitamins (calcitriol as well as ATRA all-trans retinoic acid, and OCT 22-oxacacitriol) partially compensated the negative effects of entrectinib and M5 on mineralized matrix.

Impurity

A GLP Genotoxicity study (Study Report 1104576) was carried out on the impurity RO7288587. a Drug Substance process development documentation was submitted in 2020 in which evaluation of the impurity was made. Entrectinib impurity RO7288587 was found not to induce mutation in five histidine-requiring strains (TA98, TA100, TA1535, TA102 and TA97) of *Salmonella typhimurium* when tested in absence and presence of rat S9 mix.

Acceptance criteria were within the specification thresholds in all synthesis step.

2.4.5. Ecotoxicity/environmental risk assessment

Substance (INN/Invented Name): Entrectinib					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 Additional study according to OECD 123 was performed at a single *p*H of 7	*p*H 5 logD_{OW} = 2.7 *p*H 7 logD_{OW} = 4.3 *p*H 9 logD_{OW} = 5.1 *p*H 7 logD_{OW} = 4.43			Potential PBT (Y)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation					
	BCF	BCF_{SS} = 348 L/kg BCF_K = 217 L/kg			not B .
Persistence	DT50 or ready biodegradability (OECD 307/308)	$DT_{50, sediment, 12 °C}$ = 443 d $DT_{50, whole system, 12 °C}$ = 268 d $DT_{50, soil}$ > 10.000 d			vP
Toxicity	NOEC	NOEC = 0.00606 mg/L (Fish, ELS OECD 210)			T
PBT-statement:	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.013 (refined – prevalence data)	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	Koc >> 4.27×10^5 (Capacity factor far outside of calibration curve)			OECD 106 not possible because of low solubility.
Ready Biodegradability Test	OECD 301	8 % (28 d), k_{STP} (0 h^{-1})			not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water, 12 °C}$ = 1.7/2.3 d (SFO) $DT_{50, sediment, 12 °C}$ = 443/52 d (k_2, HS/SFO) $DT_{50, total system, 12 °C}$ = 268/10,4 d (k_2, HS/SFO) % shifting to sediment = 61.5/66.2 % Transformation product >10 %: U8 (not identified)			vP
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *OECD 210/Desmodesmus subspicatus*	OECD 201	NOEC	197	µg/L	geometric mean measured concentration (GMC)

A *daphnid acute immobilisation test* according to OECD 202 (For classification and labelling purposes)	OECD 202		24 and 48 hours EC50 values were >0.266 and >0.278 mg/l GMC		*Daphnia magna*
Daphnia Reproduction Test/ *Daphnia magna*	OECD 211	NOEC	134	µg/L	(TWA)
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 210	NOEC	6.06	µg/L	(MMC)
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1,000,000	µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF_{SS} BCF_K BCF_{SSL} BCF_{KL}	348 217 116 72.4	L/kg	%lipids: 15.0 %lipids: 5.0
Aerobic and anaerobic transformation in soil	OECD 307	$DT_{50,\ 20\ °C}$ = 10000 d (k_2, DFOP) Mineralisation= 1.2 % $NER_{max\ =\ test\ end}$ = 41,6 % at 120 d Transformation product >10 %: U11 (not identified)			[^{14}C]-labelled compound only used in one soil. Problems due to low solubility.
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	< 25 % effect		mg/ kg	
Terrestrial Plants, Growth Test/*Brassica napus, Pisum sativum, Solanum lycopersicum, Cucumis sativus*	OECD 208	NOEC	1,000	mg/ kg	
Earthworm, Acute Toxicity Test/*Eisenia andrei*	OECD 207	NOEC	100	mg/ kg	dw
Collembola, Reproduction Test/*Folsomnia candida*	OECD 232	EC_{10}	108.9	mg/ kg	dw
Sediment dwelling organism	OECD 218	NOEC *(corrected to 10% Corg)*	5682	mg/ kg	*Chironomus riparius*

2.4.6. Discussion on non-clinical aspects

Subsequent addenda were submitted to extend the marketing authorization (MA) for Rozlytrek, providing new nonclinical information. A biochemical kinase inhibition profile assessment was performed on entrectinib and its metabolite M5, evaluating their potency against 11 kinases, including anti-target kinases. Results showed that entrectinib had varying potencies against anti-target kinases, while its activity against target kinases remained consistent. M5 also exhibited similar, albeit weaker, potencies against these kinases. However, no cellular evidence validating these findings has been established.

In a new study on secondary pharmacodynamics, the interaction of entrectinib and M5 was assessed at clinically relevant concentrations for specific targets. The study included some previously unassessed targets. The likelihood of entrectinib or M5 interacting with these targets at clinically relevant concentrations was considered low, and no updates to the product information were deemed necessary.

Regarding the distribution of entrectinib, a follow-up study was conducted to confirm plasma, brain, and tumour pharmacokinetic data using a mouse model. Data were only provided for the 5 mg/kg BID dose regimen: no specific justification was provided on why this dose level was selected. The new data demonstrated that both entrectinib and M5 had the highest concentrations in the tumour, suggesting a favourable dose-dependent relationship in the TRK-dependent tumour model.

On the contrary, the unexpected higher concentrations of M5 in brain tissue at 5 mg/kg BID doesn't exclude an implication of the contribution of M5 on neuro-developmental impairment observed in paediatric patients ("neuro-developmental impairment in paediatric patients" is a potentially important risk in the RMP).

These findings, together with the very low safety margins observed in the initial toxicology studies, particularly those involving juvenile rats at 4 (PNDs 7-34 – Initial Study Report 1087703) and 13 (PNDs 7-97 – Initial Study Report 1087245) weeks were considered and taken into account when determining the appropriate dosage for paediatric population.

From new in vitro PK studies in human liver microsomes show that:

-similarly to entrectinib, M5 is metabolized mainly by CYP3A isoforms and especially CYP3A4

-CYP3A4 is the main CYP3A isoform involved in the metabolism of entrectinib and M5 in adults but no conclusion can be made on their metabolism in paediatric subjects since only one paediatric liver microsomes donor was included in the study.

-Ketoconazole is the most effective inhibitor of CYP3A4/5, confirming what already known from clinical trials (see SmPC section 4.5).

- entrectinib is expected to be a very weak time dependant inhibitor on CYP3A4.

Toxicology in vitro data have been focusing on the effect of entrectinib and M5 on osteoblast+ osteoclast function, Concentrations of entrectinib and M5 up to 100 nM (lower than the clinical Cmax –1053 nM and 2075 nM (capsules) and 2032 nM and 836 (coated granules, all paediatric ages) for entrectinib and M5 respectively, were found to dose-dependently decrease osteoblast function and stimulate osteoclastogenesis in all 3 co-cultures, suggesting that the effect on the juvenile bone does not differ from that on the adult one. Overall, the effect on osteoblast function was less pronounced than that on osteoclast function.

Co-application of calcitriol may be an option to prevent spontaneous fractures in children receiving entrectinib treatment. No clinical evidence is present yet, that vitamin D3 supplementation effectively prevent low impact fractures in cancer patients. Therefore, further investigations are needed to identify the clinical effect of vitamin D3 in these patients.

Regarding entrectinib impurity RO7288587, acceptance criteria were within the specification thresholds in all synthesis step, moreover lack of genotoxicity was already declared by the Company.

ERA

Entrectinib is not PBT nor vPvB. On the basis of the prevalence of the sought additional conditions, the recalculated PECsurfacewater (i.e. 0.013 µg/L) is close to the one calculated at the time of initial approval of Rozlytrek (i.e. 0.012 µg/L). Thus, the additional therapeutic indication is not expected to pose a risk to the environment.

Preparation and use of the nasogastric or oral suspension (in water or milk):

Table 11 in section 6.6 of the SmPC shows how to prepare the suspension based on the prescribed dose to be given. A certain amount of suspension should systematically be discarded (from a minimum of 0.5 ml to a maximum of 4.5 ml) since just a part of the suspension is to be withdrawn and administered (except the cases in which the entire content of the capsule should be administered); moreover, there are other situations in which the suspension should be discarded, e.g. if the suspension is not used within 2 hours or in case the contents of the capsule are spilled outside of the cup during the preparation.
Although a general sentence ("Any unused medicinal product or waste material should be disposed of in accordance with local requirements") is reported in section 6.6, the risk of a discard in the household waste cannot be excluded also considering that the suspension is to be prepared every day. In addition to the already reported general sentence on disposal, clearer instructions on the need to avoid discarding the remaining oral suspension in the wastewater has been included in the SmPC/PL.

2.4.7. Conclusion on the non-clinical aspects

The non-clinical data support the application for an extension of the indication of Rozlytrek in solid tumours with NTRK gene fusion to patients from 1 month to 12 years of age.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Protocol No.	Location of Synopsis/ Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.1 Biopharmaceutic Studies								
GP41048	Synopsis GP41048 CSR GP41048	BA	Phase I, open-label, two-treatment, two-period, two-way crossover Study	Single PO dose 600 mg entrectinib (fed) F1 and F06 in separate periods, respectively.	N = 14	HV	Single dose with a washout period of at least 14 days	Completed; Final
GP41341	Synopsis GP41341 CSR GP41341	BA	Phase I, open-label, randomized, 2 part, 2 period	Part 1: Single PO dose of 600 mg entrectinib (fed) F06, F15 and F16 in separate periods, respectively. Part 2: Single PO dose of 200 mg entrectinib (fasted) F06 (coarse [unmilled] and F06 (fine [milled] API)	Part 1 N = 15 Part 2 N = 15	HV	Single dose with a washout period of at least 14 days	Completed; Final
GP44192	No synopsis available CSR GP44192	BA	Phase I, open-label, randomized 2-part, five treatment, 3-way	Part 1: Single PO dose of 600 mg entrectinib F06, NG suspension in water F06, PO suspension in milk F06 in separate periods, respectively. Part 2: Single PO dose of 600 mg entrectinib F06, PO suspension in water F06, PO suspension in water F06 + PPI in separate periods, respectively.	Part 1 N = 16 Part 2 N = 15	HV	Single dose with a washout period of at least 14 days	Completed; Data Memo
1101993: The LC/MS/MS Quantitation of RXDX-101 and its Metabolite RXDX-101-M5 in Human Plasma	No synopsis available BAR	NA	NA	NA	NA	NA	NA	Full
5.3.3 Human PK Studies								
Population PK and PK/PD Report (1121816)	Pop PK Report	Population pharmacokinetic, exposure-efficacy and exposure-safety relationships	NA	NA	NA	Patients with advanced/ metastatic solid tumors	NA	popPK report
Physiologically-Based PK Modelling Report (1119857)	Physiologically Based PK Report	DDI assessment and Pediatric dose recommendation	NA	NA	NA	NA	NA	PBPK report
PBPK Gastro Plus (1113585)	PBPK Report	NA	NA	NA	NA	NA	NA	PBPK report

5.3.5 Efficacy and Safety Studies								
STARTRK-NG (CO40778)	Synopsis CO40778 CSR CO40778	Efficacy, safety, PK	Phase I/II open-label, dose escalation, and expansion	**Phase I:** Doses 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	N = 68	Pediatric patients with locally advanced or metastatic solid or primary CNS tumors	Until clinical, laboratory or radiographic evidence of progressive disease, development of unacceptable toxicity, or discontinuation at the discretion of patient/parent/guardian or investigator	Ongoing; Full
TAPISTRY (BO41932)	No synopsis available Data Memo BO41932	Safety, efficacy, PK	Phase II, global, multicenter, open-label	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	N = 6	Pediatric patients with *NTRK* or *ROS1* fusion-positive tumors	Until disease progression, loss of clinical benefit, unacceptable toxicity, patient or physician decision to discontinue, or death	Ongoing; Data Memo
STARTRK-02 (GO40782)	No synopsis available Data Memo GO40782	Efficacy, safety, PK	Phase II, global, multicenter, open-label	600 mg PO daily	N = 2	Pediatric patients with locally advanced or metastatic solid tumors that harbor *ROS1* gene rearrangement	Until documented radiographic progression as assessed by investigator and/or blinded independent central review, development of unacceptable toxicity, or withdrawal of consent	Ongoing; Data Memo
Bone Fracture Report (Phase I to III) (1121210)	No synopsis available Bone Fracture Report	Bone fractures	NA	NA	NA	Pediatric patients	NA	Completed; Full
Natural History Study (SG43536)	No synopsis available CSR SG43536	To characterize the natural history of pediatric patients with solid tumors harboring an NTRK gene fusion and treated with historical standard of care (non-targeted) therapies	NA	NA	N = 13	Pediatric patients	NA	Completed; Full

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Bioanalytical methods

The bioanalytical assay used for entrectinib and M5 determinations was a LC-MS/MS and the validation reports were submitted in the initial MA. The same method has been used to measure entrectinib and M5 concentrations through the current clinical development

PK samples collected in Study STARTRK-NG were measured at Syneos and the method validation report (1101993) for the LTS validation performed at Syneos was submitted in the current variation. The validated LTS is 533 days for entrectinib and 417 days for M5 when stored at -80°C in human plasma. As reported in the BA report 117085-csr-co40778-1625, out of 1221 samples were analysed, 24 samples were analysed outside the LTS for M5 and no result was reported. Five samples have numeric results, but their results can only be considered as exploratory results for both analytes. All remaining samples were analysed within 417 days after collections, therefore within the validated LTS.

Formulations

The F06 capsule formulation (containing an alternative pH-modifier (tartaric acid) developed to facilitate manufacturing of commercial-scale batches introduced for clinical supply in Q3 2018) was introduced in the paediatric Study CO40778 (STARTRK-NG) on 13 June 2019 and since then a total 25 paediatric patients have received the capsule formulation (F06), of which 6 patients received entrectinib suspension via nasogastric administration.

Entrectinib drug substance can exist as two polymorphic forms (Form A and Form C). In 2019, the polymorphic form of entrectinib in F06 was changed from A to C. The two corresponding drug product variants (Form A and Form C) were evaluated in Study GP41049 submitted during the review of the initial MA and were considered equivalents and therefore interchangeable.

Bioequivalence

In the current variation a new route of administration of F06 capsule is proposed for patients who are unable to swallow whole capsules but able to swallow liquids or patients who require enteral administration. The capsule formulation (F06) may be prepared as an oral suspension in milk or water and administered via oral syringe or gastric/nasogastric tube. This method and route of administration are currently used in Study CO40778 (STARTRK-NG) and Study BO41932 (TAPISTRY).

A relative two-part, open-label, comparative, single-dose, randomized, five-treatment, three-way crossover sequential bioavailability study (GP44192) was conducted to assess the relative bioavailability of entrectinib whole capsule compared to nasogastric and oral administration of suspension (in water and milk) in healthy subjects.

The study also aims to assess the effect of lansoprazole on entrectinib exposure following oral co-administration of lansoprazole tablet with entrectinib suspension in water (test) compared to administration of entrectinib suspension in water alone (reference).

This study also aimed to assess the palatability of both oral suspensions in water and milk.

Entrectinib 600 mg dose was used.

In Part 1, the F06 whole capsules (reference treatment C) were compared with nasogastric administration of suspension in water (Treatment A, test) and with the oral administration of suspension in milk (Treatment B, test).

PK samples were available for 15, 16 and 13 subjects for NG suspension, oral suspension in milk and F06 whole hard capsules, respectively.

In Part 2, the F06 whole capsules were compared with oral administration of suspension in water (Treatment D, test) and with oral co-administration of lansoprazole tablet plus entrectinib suspension in water (Treatment E, test). 15 subjects completed the Part 2.

In Period 3, all subjects took part in a fixed treatment (Treatment E).

The primary outcome measures were:

1. Maximum observed plasma concentration (Cmax) of entrectinib and M5 (its metabolite) measured from blood samples collected at pre-dose and multiple timepoints up to 96 hours post entrectinib administration in each of the three periods (1, 2 and 3) in both Part 1 and Part 2

2. Area under the plasma concentration versus time curve from time zero extrapolated to infinity (AUC0-inf) of entrectinib and M5 (its metabolite) measured from blood samples collected at pre-dose and multiple timepoints up to 96 hours post entrectinib administration in each of the three periods (1, 2 and 3) in both Part 1 and Part 2

NG administration of oral suspension versus F06 hard capsules: statistical analysis of the PK parameters showed that systemic exposure to entrectinib was similar following NG administration of entrectinib suspension in water (test) and oral administration of entrectinib hard capsules (reference), with geometric mean ratio (GMR) (90% CI) values of 99.0 (84.7, 116) for Cmax, 104 (86.8, 124) for AUC0-t, and 104 (87.1, 125) for AUC0-inf. Statistical analysis for M5 showed similar exposure between the two modes of administration of the capsules.

Oral suspension in milk versus F06 hard capsules: statistical analysis of PK parameters showed that Cmax of entrectinib was higher (GMR [90% CI] of 124 [106, 145]), and AUC0-t and AUC0-inf were similar (GMR [90% CI] of 114 [95.2, 136] and 113 [94.3, 135]).

The 90% CIs of the GMRs for entrectinib Cmax, AUC0-t, and AUC0-inf were outside the range of 80% to 125% for the comparison of oral administration of entrectinib suspension in milk (test) to oral administration of entrectinib hard capsules (reference).

Systemic exposure to M5 was higher following oral administration of entrectinib suspension in milk (test) compared to oral administration of entrectinib hard capsules (reference; GMR [90% CI] values for Cmax, AUC0-t, and AUC0-inf of 148 [119, 184], 139 [117, 164], and 132 [112, 154], respectively).

Oral suspension in water versus F06 hard capsules: statistical analysis of the PK parameters showed that entrectinib AUC0-t and AUC0-inf were similar (GMR [90% CI] of 90.2 [81.4, 100] and 91.3 [82.4, 101], respectively) and entrectinib Cmax was lower (19%) (GMR [90% CI] of 81.4 [71.6, 92.5]) following oral administration of entrectinib suspension in water (test) compared to oral administration of entrectinib hard capsules (reference). The 90% CIs of the GMRs for entrectinib AUC0-t and AUC0- were within 80% and 125% whereas the 90% CI of the GMR for entrectinib Cmax was outside this boundary.

Statistical analysis of the PK parameters showed that AUC0-t and AUC0- for M5 were similar following oral administration of entrectinib suspension in water (test) compared to oral administration of entrectinib hard capsules (reference; GMR [90% CI] of 85.3 [66.6, 109] and 87.9 [70.1, 110], respectively) while Cmax of M5 was lower (GMR [90% CI] of 73.1 [54.6, 97.9]).Oral suspension in water + lansoprazole versus F06 hard capsules: statistical analysis of PK parameters showed that the AUC0-t and AUC0-inf were slightly higher (GMR [90% CI] of 113 [103, 125] and 114 [103, 125], respectively) while Cmax was similar (GMR [90% CI] of 94.2 [86.9, 102]) following oral co-administration of lansoprazole tablet with entrectinib suspension in water (test) compared to oral administration of entrectinib hard capsules (reference).

Although this study was not powered, the 90% CIs of the GMRs for entrectinib Cmax, AUC0-t, and AUC0- were within 80% and 125% when comparing oral co-administration of lansoprazole tablet with entrectinib suspension in water (test) to oral administration of entrectinib hard capsules (reference).

The AUC0-t and AUC0- of M5 were similar (GMR [90% CI] of 90.7 [76.8, 107] and 93.1 [79.0, 110], respectively) while Cmax was lower (GMR [90% CI] of 66.9 [53.4, 84.0]) following oral co-administration of lansoprazole tablet with entrectinib suspension in water (test) compared to oral administration of entrectinib hard capsules (reference).

Oral suspension in water + lansoprazole versus oral suspension in water without lansoprazole: the statistical analysis showed that Cmax and AUCs of entrectinib were slightly higher following oral co-administration of lansoprazole tablet with entrectinib suspension in water (test) compared to oral administration of entrectinib suspension in water (reference), with GMR (90% CI) values for Cmax, AUC0-t, and AUC0- of 117 (104, 132), 126 (110, 145), and 125 (108, 144), respectively.

The Cmax, AUC0-t, AUC0- of M5 were similar between treatments with GMR (90% CI) values of 92.9 (78.8, 110), 108 (94.0, 124), and 108 (94.9, 122), respectively. In general, low within-subject variability was noted for Cmax, AUC0-t, and AUC0- with values of 19.2%, 22.3%, and 22.3%, respectively, for entrectinib and 26.0%, 21.7%, and 19.7%, respectively, for M5.

Palatability of the oral suspension:

For the suspension in milk, the 50% of participants rate as unpleasant the after taste and the texture of suspension in milk, 43.8% rate as unpleasant the feeling when swallowing, 93.8% would take the drug again. The suspension in water seems more acceptable than the suspension in milk, with 40% rating as unpleasant the aftertaste and mouth feel; however, 86.7% would take the drug again

Coated granules:
In addition to the new route of administration for F06 capsules, a coated granule formulation for paediatric patients with difficulty swallowing capsules was developed to be sprinkled over soft food. The coated granule formulations (**F15** and **F16**; containing the same Form A but a different coating) were compared to the approved F06 capsule formulation in a relative bioavailability study (Study GP41341).

Study GP41341 was a randomized, open-label, single-center, two-part study in healthy volunteers (N=15 Part 1 and N=6 Part 2) to explore the performance of entrectinib coated granule formulations compared to the F06 capsule formulation (**Part 1**) and the effect of drug substance particle size on entrectinib bioavailability in the F06 capsule formulation (Part 2). The principal aim of the second part of this study was therefore to explore the effect of drug substance particle size on entrectinib bioavailability by comparing entrectinib exposures from two F06 capsule formulations containing coarse (unmilled) and fine (milled) drug substance with different particle size distributions. This study was submitted within the initial marketing authorisation.

An additional objective for this study was to explore the palatability (taste and acceptability) of coated and uncoated multi-particulate formulations on the basis of palatability questionnaire.

Part 1 was a three-treatment, three-period, three-sequence, three-way crossover design. In each treatment period, subjects received a single 600-mg oral dose of entrectinib under fed conditions. Entrectinib was administered as one of three possible formulations:

- Coated granule formulation 1: Entrectinib film-coated granules (non-functional coating, F15 aesthetic coating), 600 mg (240 x 2.5 mg [**F15**] test formulation 1 [T1])

- Coated granule formulation 2: Entrectinib film-coated granules (functional coating for taste masking), 600 mg (240 x 2.5 mg [Ro 710-2122/**F16**]; test formulation 2 [T2])
- F06 capsule formulation: Entrectinib (RXDX-101) **F06** hard capsules (3 x 200 mg [Ro 710-2122/F04]; reference formulation [R]).

Entrectinib was given with food in order to match dosing instructions for patients in pivotal and supportive clinical trials, which recommend administering entrectinib within 30 minutes following a meal.

Fifteen subjects were randomized, dosed, and completed Part 1 of the study. Five subjects were randomized to each of the three treatment sequences (T1T2R, T2RT1 and RT1T2).

Subjects aged between 18 and 60 years. Most (11; 73.3%) subjects were male, and 4 (26.7%) subjects were female. Most (14; 93.3%) subjects were White and 1 (6.7%) subject was Asian.

The results for the formal statistical analysis of entrectinib Cmax, AUC0-t and AUC0-inf assessing the relative bioavailability of test vs reference (F15 vs F06 and F16 vs F06) are summarized in Table 5.

Table 3: Summary of Plasma Pharmacokinetic Parameters and Relative Bioavailability Assessment for Entrectinib from F15 and F16 Mini- tablet Formulations and Reference F06 Capsule Formulations Administered with Food: Pharmacokinetic Population — Part 1

Formulation	F06 capsule	F15 mini-tablet	F16 mini-tablet	Ratio between treatment means (%) (90% CI)[a]	
No. of Subjects Parameter	N=15	N=15	N=15	F15 vs F06	F16 vs F06
T_{max}[b] (h)	5.000 (3.00-12.02)	5.000 (1.98-5.10)	5.000 (3.00-6.00)		
C_{max} (nmol/L)	1880 (26.1%)	1930 (24.9%)	1940 (21.3%)	103.08 (95.17, 111.65)	103.51 (95.57, 112.11)
AUC_{0-t} (nmol.h/L)	41300 (38.5%)	40600 (36.5%)	43200 (30.9%)	98.39 (89.48, 108.20)	104.73 (95.24, 115.17)
AUC_{0-inf} (nmol.h/L)	43400 (40.9%)	41500 (38.2%) [n=14]	46600 (34.5%) [n=14]	97.57 (88.00, 108.17)	107.56 (97.01, 119.25)
$T_{1/2}$ (h)	20.809 (19.3%)	20.873 (17.0%) [n=14]	23.117 (19.8%) [n=14]		

[a] F06 is the reference formulation for all analyses.
[b] Median (range); all other parameters are presented as Geometric means (CV%).
Source: Data from Table 14.2.1.2.1 dated 08 Oct 2019 11:03 and Table 14.2.1.3.1, dated 07 Oct 2019 14:03
Results obtained from mixed effects model of natural log transformed PK parameters including terms for treatment, period and sequence fitted as fixed effects and subject nested within sequence fitted as a random effect.

M5 GMR (90% CI) between F15 and F06 for Cmax was 110.51 (97-125.90), for AUC0-t was 101.18 (91.51-111.86).

GMR for entrectinib and M5 fall within the confidence interval to establish the BE.

The F15 (Form A) coated granule formulation was introduced in Study CO40778 (STARTRK-NG) and data from 15 patients are available based on a clinical cutoff date (CCOD) of 02 August 2022. The coated granule formulation has also been introduced in the paediatric clinical Study BO41932 (formerly TAPISTRY). The proposed commercial coated granule formulation (**F17**) contains entrectinib polymorphic Form C. Three subjects in STARTRK-NG were dosed with F17.

There is no relative bioavailability study conducted between coated granules (F15 Form A) and coated granules (F17 Form C).

A Virtual BE was also submitted based on an extension of a previously described physiologically based pharmacokinetic (PBPK; Parrott et al. 2020) model (in GastroPLUS) to allow simulations for entrectinib capsule and coated granule formulations to support extrapolation of fed state bioequivalence to fasted state. In particular, the published PBPK was modified to include additional mechanistic and quantitative data on the adsorption and metabolism of entrectinib and M5, its major equipotent active metabolite. A full PBPK model for entrectinib was linked to a full PBPK model for M5. Measured in vitro biorelevant dissolution versus time profiles for the fasted state were implemented in the final version of the model. Based on in vitro results, the intestinal and hepatic metabolism was mainly attributed to the CYP3A4 enzyme; the fraction forming M5 was ¾ of the total hepatic CYP3A4 metabolism. This updated PBPK was validated for fasted state bioequivalence simulations using clinical data for F06 and F2A formulations administered in the fasted state. After incorporating fasted dissolution data for the coated granules, VBE simulations were performed for the coated granules versus the marketed capsule. All the simulations were performed using GastroPlus V9.8.3.

Palatability of the coated granules: The palatability questionnaire was administered to subjects included in the Part 1 of Study GP41341.

The age ranged from 18 to 60 years old and F15 and F16 granules (240 × 2.5 mg granules) were sprinkled on to, and mixed with, one tablespoon (15 mL) of yogurt, which was swallowed without chewing with approximately 240 mL of water.

Overall palatability VAS scores ranged from 4 to 94 mm for the F15 granules formulation and from 6 to 100 mm for the F16 granules formulation; the median scores were 39.0 mm and 69.0 mm for the F15 and F16 granules formulations, respectively.

Overall the responses to questions about the experience of taking the granules were generally neutral (i.e., most median scores were approximately 50 mm). No intense initial taste or aftertaste was reported by the majority of subjects. Where an initial taste was reported, the descriptors with the highest median VAS scores were sour and sweet for the F15 and F16 granules formulations, respectively. Few subjects (3 out of 15 subjects and 2 out of 15 subjects for the F15 and F16 granules formulations, respectively) reported experiencing residual bits or lumps in the mouth after swallowing, and most participants (12 out of 15 subjects for both formulations) indicated a willingness to take the medicine again.

Updated paediatric data

Within this variation, and respect to the initial authorisation procedure (see EPAR) new PK analysis have been performed in children, adolescents, and young adult patients with new data obtained from the updated Study CO40778 (STARTRK-NG) pooled with data from previous report of Study GO40782 (STARTRK-2; RXDX-101-02) and Study BO41932 (TAPISTRY).

The main amount of PK data is derived from STARTRK-NG study (about 60 patients treated with different doses and formulation/route of administration), in addition PK data are available from two paediatric patients enrolled in Study GO40782 (STARTRK-2; RXDX-101-02) and from four paediatric patients enrolled in study BO41932 (TAPISTRY).

Non-compartmental analysis was performed for Study STARTRK-NG, moreover a popPK analysis was developed including all available paediatric data. NCA was performed at Cycle 1 day 1 (after single dose) and Cycle 2 day 1 (steady state).

Table 4: Summary Of the Sum (Entrectinib and M5) Exposure Parameters after a Single Dose Of Entrectinib by Nominal Dose (Day 1 Of cycle 1)

Formulation	Dose (mg/m^2)	Day 1	
		C_{max} (nM)	AUC_{24} (h*nM)
F1 – capsule N=12	550	4024 (59.4%)	54490 (61.8%)
F1 – open N=9	400	2471 (40.8%)	33530 (46.2%)
F06 – capsule N=9	300	2350 (47.0%)	33679 (47.03%)
F06 - NG N=5	250	1678 (140%)	19619 (113%)
F06 – NG N=1 (> 12 years old)	300	3270*	54562*
coated granules (F15 + F17) N=9	300	1826 (42.1%)	24089 (39.8%)
coated granules (F15 + F17) N=7 (> 1 year old)	300	2087 (33.6%)	27592 (29.9%)
F15 – coated granules N=2 (≤ 1 year old)	300	1430*, 915*	18374*, 12207*
F17 coated granules (Form C) N=1	300	2665*	37644*

AUC_{24} = area under the plasma concentration-versus-time curve from time 0 to 24 hours;
C_{max} = maximum concentration; N = number; NG = nasogastric.
Geometric mean (CV%).
*Individual value
Two patients were excluded from analysis due to erratic PK profile and insufficient number of samples.
One patient had no M5 values reported.

Table 5: Summary of Geo. Mean (geoCV%) PK Parameters for Entrectinib and M5 Following a Multiple Dose of Entrectinib by Nominal Dose (mg/m2) (Phase II; Day 1 of Cycle 2; Steady State for Formulation Switch)

	Entrectinib (Day 29)				M5 (Day 29)			
Formulation / Dose (mg/m^2)	**N**	**C_{max} (nM)**	**AUC_{0-24} (nM•h)**	**Racc**	**C_{max} (nM)**	**AUC_{0-24} (nM•h)**	**Racc**	**AUC_{0-24} M/P ratio**
F1–whole capsule / 550	8	3244 (39.5%)	54562 (43.0%)	1.33 (65.8%)	1070 (48.0%)	20860 (42.7%)	1.52 (70.9%)	0.38 (42.1%)
F1–open capsule / 400	7	2061 (48.7%)	29740 (64.7%)	1.38 (69.2%)	577 (64.5%)	9226 (66.0%)	1.03 (78.4%)	0.31 (88.6%)
F06–whole capsule / 300	12	1988 (30.1%)	32138 (34.1%) N=11	1.27 (67.8%) N=8**	583 (45.9%)	10623 (43%) N=11	1.45 (59.4%) N=8	0.33 (55.0%) N=11
F06–NG / 250	3 (<6 mos)	1053 (93.2%)	12783 (102.6%)	1.20 (49.5%) N=3	2075 (31.0%)	34290 (42.1%)	1.90 (66.3%)	2.68 (47.0%)
F15+F17 coated granules / 300	17 (all ages)	2032 (58.3%)	25848 (79.6%)	1.28 (35.2%) N=10	836 (61.1%) N=15	13068 (57.8%) N=15	2.18 (38.2%) N=8	0.48 (107%) N=15
F15+F17 coated granules / 300	9 (>1 yrs)	2573 (38.0%)	36259 (45.4%)	1.43 (35.7%) N=8	928 (50.64%) N=8	15456 (56.7%) N=8	2.47 (33.9%) N=6	0.40 (57.1%) N=8

Table 6: Summary of the Sum (Entrectinib and M5) Exposure Parameters after a Single Dose and multiple dose of Entrectinib by Nominal Dose (Day I Of Cycle 2)

Formulation	Dose (mg/m^2)	Day 29 – steady state	
		C_{max}	AUC
F1 – capsule N=8	550	4361 (37.3%)	76498 (37.5%)
F1 – open N=7	400	2728 (44.0%)	41008 (51.5%)
F06 – capsule N=12	300	2611 (29.0%)	43769 (27.3%) N=11
F06 - NG N=3	250	3187 (50.2%)	47701 (56.5%)
coated granules (F15 + F17) N=15	300	3119 (38.5%)	43482 (50.4%)
coated granules (F15 + F17) N=8 (> 1 years old)	300	3757 (32.0%)	55495 (40.4%)
coated granules (F15 + F17) N=7 (≤ 1 years old)	300	2521 (34.0%)	32903 (44.5%)
F17 coated granules (Form C) N=2	300	3913*, 2938*	51288*, 30849*

AUC_{24} = area under the plasma concentration-versus-time curve; C_{max} = maximum concentration; N=number; NG = nasogastric.
*Individual value
Two patients did not have M5 reported
One patient (F06 capsule) only had C_{max} reported.
One patient was excluded from analysis due to erratic PK profile.
Five patients were excluded from analysis due to insufficient number of samples (all D29).

The geomean sum AUC (entrectinib + M5; active moieties) following single dose administration ranges from 12207 to 54490 h*nM across ages (from > 1 month to < 12 years). Sum AUC of the two active moieties was 33679 (47.0%) h*nM and 27592 (29.9%) h*nM following capsule (F06) and coated granules (F15/F17) administration, respectively. Lower systemic exposure was observed for patients < 1 year old dosed with either nasogastric administration or coated granules.

After multiple doses, entrectinib systemic exposure (AUC) was 36259 (35.7%) h*nM and 32138 (67.8%) h*nM following administration with coated granules (F15/F17) and capsule (F06) administration, respectively for patients > 1 year old. Entrectinib systemic exposure was comparable between coated granules (F15/F17) and capsule (F06) for patients ≥ 1 year old. Paediatric patients between the age of 6 months and 1 year dosed with coated granules showed lower entrectinib exposure compared to older children.

On the other hand, entrectinib systemic exposures appeared to be lower (12783 (49.5%) h*nM) in patients < 6 months following nasogastric administration compared to patients dosed orally with the capsule formulation (F06) (32138 (67.8%) h*nM). In addition, most patients receiving nasogastric administration were <6 months and received the dose of 250 mg/m2, except for one patient who was 7 years old.

Dose recommendations

Within this variation the MAH proposed the following dosing regimen, based on population PK analysis of paediatric and adult pharmacokinetics (PK) and exposure-response data and PBPK analysis:

Below 6 months

Age	Once Daily Dose[a]
newborn – ≤ 1 month[b]	100 mg/m^2
> 1 month to ≤ 6 months[c]	250 mg/m^2

From 6 months

Category	Body Surface Area	Once Daily Dose
I	0.43–0.50 m^2	100 mg
II	0.51–0.80 m^2	200 mg
III	0.81–1.10 m^2	300 mg
IV	1.11–1.50 m^2	400 mg
V or adults	≥ 1.51 m^2	600 mg

The proposed dose recommendations (see table below) derived from modelling and simulation analysis obtained from PBPK model (Gastroplus 1091111 and Symcyp 1091399), updated popPK model 1121816 and updated PBPK 1119857.

The PopPK 1121816 is the updated version of the existing popPK 1091319 report (initial MA) and its aims were: (1) to evaluate the impact of patient's characteristics on the PK of entrectinib and its equally active metabolite, M5; (2) to determine individual exposure metrics to be used in the exposure-efficacy and -safety analyses; (3) to characterize the relationship between exposure of active moieties (entrectinib and M5), and efficacy outcome (responder status based on best overall response [BOR]) and safety outcomes (treatment-emergent adverse events [AEs] of grade 3 or higher, serious adverse events [SAEs], and bone fractures); (4) to support the dosing regimen recommendations of entrectinib in paediatric patients with tumours harbouring NTRK or ROS1 fusions.

Data were collected in five clinical studies: STARTRK-1 (GO40784, RXDX-101-01), STARTRK2 (GO40782, RXDX-101-02), STARTRK-NG (CO40778, RXDX-101-03), RXDX-101-14 (GO40785) and TAPISTRY (BO41932).

The PK of entrectinib was described by a one-compartment model with sequential zero- and first-order absorption processes without lag-time, and linear elimination. The parameters estimated for entrectinib were: D1, the duration of zero-order absorption; Ka, the first-order absorption rate constant; CL/F, the apparent clearance; and V/F, the apparent volume of distribution. The PK of M5 was characterized with a one-compartment model with linear elimination. The estimated parameters were: CLM/F, the apparent clearance, VM/F and the apparent volume of distribution.

The model assumed that all entrectinib was metabolized into M5.

The residual unexplained variability (RUV) was modelled as a combination of an additive and a proportional error for each entity. The popPK analysis was performed using NONMEM program version 7.4.3 (ICON Development Solutions, Ellicott City, MD) and R version 4.1.3 (R Core Team 2009) was used as supportive software for descriptive statistics, figures, post-processing of the results, exposure-response analyses, and simulations. The significant covariates were: BW on CL/F and V/F and age on M5 clearance CLM/F, included via a maturation function. VPC and GoF were submitted for model diagnostics.

Dose reductions for tolerability

The popPK report 1121816 was used to provide a dose reduction scheme as reported in the table below based on simulation.

Table 2: Dose reduction schedule

Starting dose once daily	**First dose reduction**	**Second dose reduction**	Permanently discontinue Rozlytrek in patients who are unable to tolerate Rozlytrek after two dose reductions.
250 mg/m^2	Reduce the once daily dose to two thirds of the starting dose*	Reduce the once daily dose to one third of the starting dose*	
100 mg	50 mg or 100 mg once daily, according to schedule**	50 mg once daily	
200 mg	150 mg once daily	100 mg once daily	
300 mg	200 mg once daily	100 mg once daily	
400 mg	300 mg once daily	200 mg once daily	
600 mg	400 mg once daily	200 mg once daily	
*To enable dosing increments of 10 mg, capsules prepared as an oral suspension may be used. Refer to the Method of administration **Monday (100 mg), Tuesday (50 mg), Wednesday (100 mg), Thursday (50 mg), Friday (100 mg), Saturday (50 mg), and Sunday (100 mg).			

Simulation for the first dose reduction

Distributions of simulated steady state AUC for entrectinib, M5, and their sum for the first dose reduction in each of the category of BSA for children aged 6 months or older are summarized in Table 9, with a comparison to simulated exposures in adults (from 1000 virtual patients treated with 400 mg QD and weighing 70 kg).

Table 7: Summary Statistics Of Simulated AUCss Of Entrectinib, M5, and their Sum after the First Dose Reduction from the Proposed Dosing Algorithm for Paediatric Patients Aged 6 Months or Older

Category	BSA (m^2)	Daily dose (mg)	No. sim	Entrectinib AUCss (nM x h)	M5 AUCss (nM x h)	Sum of entrectinib and M5 AUCss (nM x h)
Adult	-	400	1000	33900 [15200-80600]	13100 [4790-36800]	47900 [22500-108000]
I	0.43-0.50	50 or 100 [a]	1028	12200 [4770-26800]	9400 [3330-24700]	22400 [9820-48000]
II	0.51-0.80	150	6203	20200 [8630-47700]	10100 [3730-27800]	31400 [14000-70200]
III	0.81-1.10	200	5859	26100 [10900-61500]	11100 [3980-31700]	38700 [16800-85900]
IV	1.11-1.50	300	6348	32800 [14100-77200]	13600 [4710-37100]	48100 [21600-107000]
V	≥1.51	400	4822	35200 [14900-83300]	14000 [5190-39400]	50900 [22600-116000]

[a] According to the following schedule: Monday (100 mg), Tuesday (50 mg), Wednesday (100 mg), Thursday (50 mg), Friday (100 mg), Saturday (50 mg), Sunday (100 mg).
BSA, body surface area; No. sim, number of simulated individual; AUCss, steady state area under the concentration time curve.
Statistics are shown as median [5th percentile-95th percentile].
Source: /_Projects/RO7102122_Solid tumor_30226/PopPK/Filing_peds_popPK-ER/Step 12/figures_exposure_peds_simulations_global-filing_1st-dose-reduction.docx

As for the starting dose, simulated exposures of entrectinib and M5 for BSA categories III, IV, and V (i.e. >0.80 m^2) were in the range of adult exposures. For category II, exposure of entrectinib tends to be lower than in adults, resulting in a median sum of entrectinib and M5 AUCss of 31400 nM x h (90% PI: 14000-70200) versus 47900 nM x h (90% PI: 22500-108000) in adults (i.e. ~66% of the adult value). This difference is also present for category I, with a median sum of entrectinib and M5 AUCss of 22400 nM x h (90% PI: 9820-48000; ~47% of the adult value).

Simulation for the second dose reduction

Distributions of simulated steady state AUC for entrectinib, M5, and their sum for the first dose reduction in each of the category of BSA for children aged 6 months or older are and summarized in Table 10, with a comparison to simulated exposures in adults (from 1000 virtual patients treated with 200 mg QD and weighing 70 kg).

Table 8: Summary Statistics Of Simulated AUCss Of Entrectinib, M5, and their Sum with the Second Dose Reduction from the Proposed Dosing Algorithm for Paediatric Patients Aged 6 Months or Older

Category	BSA (m^2)	Daily dose (mg)	No. sim	Entrectinib AUCss (nM x h)	M5 AUCss (nM x h)	Sum of entrectinib and M5 AUCss (nM x h)
Adult	-	200	1000	16900 [7600-40300]	6550 [2390-18400]	24000 [11300-54200]
I	0.43-0.50	50	1028	6090 [2380-13400]	4700 [1670-12300]	11200 [4910-24000]
II	0.51-0.80	100	6203	13500 [5750-31800]	6750 [2490-18500]	20900 [9330-46800]
III	0.81-1.10	100	5859	13100 [5460-30700]	5530 [1990-15800]	19300 [8390-42900]
IV	1.11-1.50	200	6348	21900 [9400-51500]	9060 [3140-24700]	32100 [14400-71100]
V	≥1.51	200	4822	17600 [7440-41500]	7010 [2600-19700]	25400 [11300-58100]

BSA, body surface area; No. sim, number of simulated individual; AUCss, steady state area under the concentration time curve.
Statistics are shown as median [5th percentile-95th percentile].
Source: /_Projects/RO7102122_Solid tumor_30226/PopPK/Filing_peds_popPK-ER/Step 12/figures_exposure_peds_simulations_global-filing_2nd-dose-red.docx

Overall, simulated exposures of entrectinib and M5 for BSA categories II, III, and V were in the range of adult exposures. For category IV (BSA of 1.11-1.50 m2), a tendency to larger exposure of entrectinib and M5 compared to adults is expected, resulting in a median sum of entrectinib and M5 AUCss of 32100 nM x h (90%PI: 14400-71100) versus 24000 nM x h (90%PI: 11300-54200) in adults (~33% larger).
For category I (BSA range: 0.43-0.50 m2), exposure of entrectinib and M5 tends to be lower than in adults, resulting in a median sum of entrectinib and M5 AUCss of 11200 (90% PI: 4910-24000; ~47% of the adult value).

In silico DDI data

No dedicated DDI studies have been performed in children.

The updated version of Symcyp PBPK model (1119857) has been performed with the aim to predict the exposure changes of entrectinib and its major circulating and equally potent metabolite, M5, after multiple oral administration of entrectinib in paediatrics in the presence of either moderate or strong CYP3A4 inhibition. The PBPK model building workflow for entrectinib and M5 was refined by re-visiting the non-clinical and clinical regulatory dossiers, with the following updates: inclusion of mechanistic absorption model components for entrectinib, refinement of the drug dispositions of entrectinib and M5, especially regarding the intestinal and hepatic metabolism via CYP3A4 to allow consideration of the maturational changes in CYP3A4. SimCYP Population-based Simulator, Version 21 (Certara Inc., Princeton, NJ) was used for all simulations. The verification of PBPK was performed using data from Study RXDX-101-12 (DDI study) and observed exposure in children.

2.5.2.2. Pharmacodynamics

One of the aims of PopPK analysis (1121816) was to characterize the relationship between exposure of active moieties (entrectinib and M5), and efficacy outcome (responder status based on best overall response [BOR])

and safety outcomes (treatment-emergent adverse events [AEs] of grade 3 or higher, serious adverse events [SAEs], and bone fractures).

E-R models were fitted to the data using logistic regression models in order to characterize the relationship between entrectinib and efficacy or safety outcomes in the patient population at various dose/exposure levels.

The evaluation of the relationship between exposure of entrectinib and M5 (i.e. their sum) and efficacy were conducted using data from 52 paediatric patients with NTRK (N=36) or ROS1 (N=16) fusion, with available secondary PK parameters, and available efficacy information from studies STARTRK-NG (N=47), STARTRK-2 (N=1), and TAPISTRY (N=4). Responders (BOR), defined as PR or CR by BICR, based on RECIST (N=17 with NTRK fusion, N=8 with ROS1 fusion) or RANO (N=19 with NTRK fusion, N=8 with ROS1 fusion), represented 23 out of 36 (64%) NTRK fusion-positive patients and 10 out of 16 (63%) ROS1 fusion-positive patients. A large overlap in the exposure metrics was determined between responders and non-responders in the NTRK fusion positive patients.

Table 9: Summary Statistics of the Sum of Steady State AUC for Entrectinib and M5 in Paediatric Patients with NTRK Fusion, by Clinical Response and Response Criteria

Responder[a]	Responder criteria	N	Mean	Standard deviation	Minimum	Median	Maximum
No	RANO	10	54500	19100	24600	57700	76000
	RECIST	3	47300	26600	17000	58500	66500
Yes	RANO	9	55000	33300	7030	48900	127000
	RECIST	14	50500	20200	29700	42300	89900

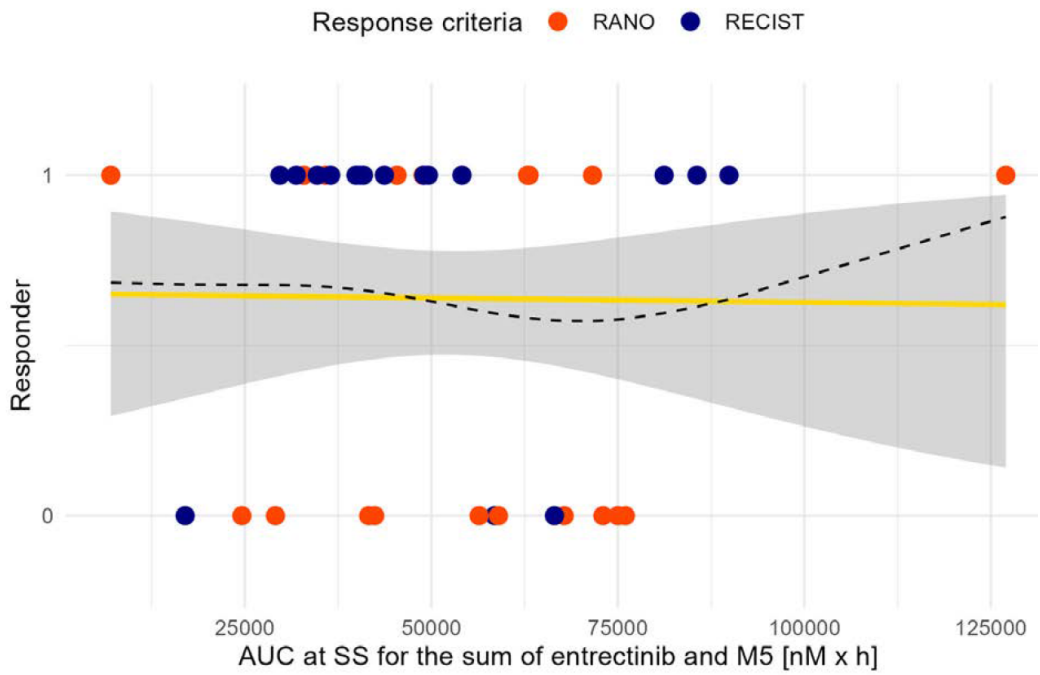
AUC, area under the concentration-time curve, nM.h; N, number of patients.
[a]Derived from the best overall response. Patients with partial response (PR) or complete response (CR) are defined as responders.
Source: TF.R

Table 10: Summary Statistics of the Sum of Steady State AUC for Entrectinib and M5 in Paediatric Patients with ROS1 Fusion, by Clinical Response and Response Criteria

Responder[a]	Responder criteria	N	Mean	Standard deviation	Minimum	Median	Maximum
No	RANO	3	66800	18500	53500	59000	87900
	RECIST	3	44500	26200	14700	54600	64100
Yes	RANO	5	83900	58700	26800	74500	168000
	RECIST	5	93200	49600	41900	93700	159000

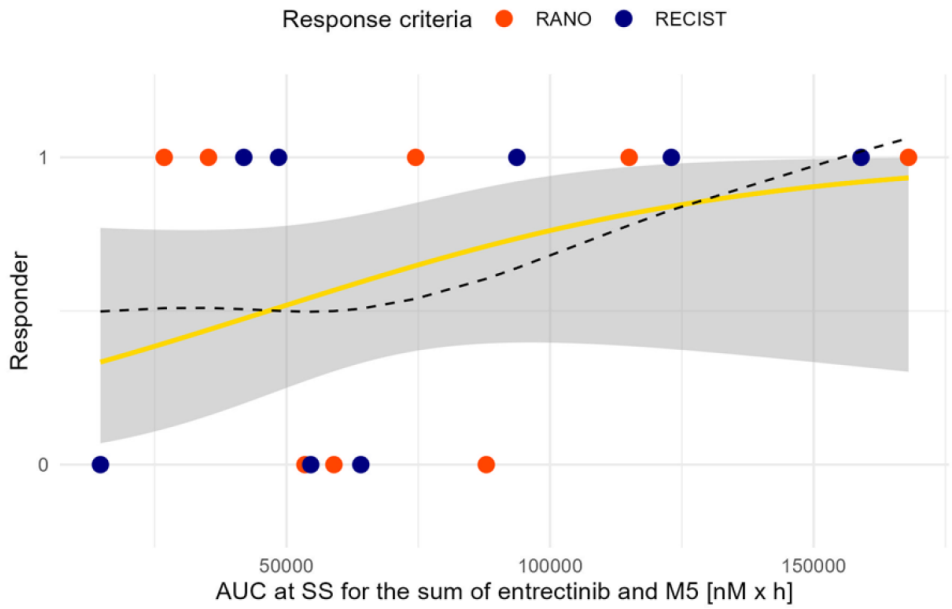
AUC, area under the concentration-time curve, nM.h; N, number of patients.
[a]Derived from the best overall response. Patients with partial response (PR) or complete response (CR) are defined as responders.
Source: TF.R

Figure 1 : Relationship between Clinical Response and Sum Of Steady State AUC for Entrectinib and M5 in Paediatric Patients with NTRK Fusion



AUC, area under the concentration-time curve, RANO, Response Assessment in Neuro-Oncology Criteria; RECIST, Response Evaluation Criteria in Solid Tumors.
Symbols: observed data. Solid yellow line and grey shaded area: smoothed line fitted to the data using a logistic regression and its corresponding 95% confidence interval. Dashed line: spline fitted to the observed data.
Source: TF.R

Figure 2: Relationship between Clinical Response and Sum Of Steady State AUC for Entrectinib and M5 in Paediatric Patients with ROS1 Fusion



AUC, area under the concentration-time curve, RANO, Response Assessment in Neuro-Oncology Criteria; RECIST, Response Evaluation Criteria In Solid Tumors.
Symbols: observed data. Solid yellow line and grey shaded area: smoothed line fitted to the data using a logistic regression and its corresponding 95% confidence interval. Red dashed line: spline fitted to the observed data.
Source: TF.R

The logistic regression models (univariate analysis) using exposure metrics (i.e. AUC and Cmax of entrectinib, M5 and their sum at SS) on normal or log10 scale did not show differences between responders and non-responders both in the NTRK and ROS1 group. Notably, most of the non-responders among NTRK fusion-positive patients consisted in patients with CNS tumours for which BOR was assessed with the RANO criteria. The STARTRK-NG (CO40778) study enrolled patients with both measurable or evaluable disease. For those patients with CNS tumours with evaluable disease only (non-target lesions), even if a complete radiographic response was observed, the overall response per RANO criteria can only be classified as stable disease. Moreover, despite the large response rate, no trend was observed between SLD dynamics and exposure groups (below vs above median) both in the NTRK (N=17) and ROS1 (N=10) patients.

Table 11: Logistic Regression Results for Best Overall Response versus Steady State Exposure (AUC and C_{max}) for the Sum of Entrectinib and M5 in Paediatric Patients with NTRK Fusion when Age is Included

Scale	Baseline age	C_{max} at SS for the sum of entrectinib and M5	AUC at SS for the sum of entrectinib and M5
Original	0.0255 (0.761)	-0.000122 (0.637)	-
Original	0.0394 (0.656)	-	-0.0000121 (0.452)
Log10	0.0314 (0.710)	-1.26 (0.477)	-
Log10	0.0450 (0.608)	-	-1.62 (0.355)

AUC = area under the concentration-time curve; C_{max} = maximum concentration; SS = steady state.
Values represent slope (p value).

Table 12: Logistic Regression Results for Best Overall Response versus Steady State Exposure (AUC and C_{max}) for the Sum of Entrectinib and M5 in Paediatric Patients with ROS1 Fusion when Age is Included

Scale	Baseline age	C_{max} at SS for the sum of entrectinib and M5	AUC at SS for the sum of entrectinib and M5
Original	-0.0483 (0.715)	0.000520 (0.114)	-
Original	-0.0432 (0.739)	-	0.0000270 (0.151)
Log10	-0.0488 (0.714)	3.80 (0.127)	-
Log10	-0.0443 (0.734)	-	3.32 (0.156)

AUC = area under the concentration-time curve; C_{max} = maximum concentration; SS = steady state.
Values represent slope (p value).

In order to better understand the between-patient variability in exposure-response relationship (efficacy), the MAH performed additional analysis (multivariate analysis). Results from the multivariate logistic regression analyses evaluating the relationship between the sum of entrectinib and M5 steady state exposure (C_{max} or AUC, either on the original or log10 scale) and best overall response when age is included in the model have been presented for both NTRK fusion-positive paediatric patients and for ROS1 fusion-positive patients. Upon inclusion of age in the logistic regression models, none of the exposure-response relationship was statistically significant. These additional analyses confirm that the between-patient variability in exposure does not explain the variability in response, and that the previous conclusion on the lack of an exposure-response relationship remain the same when considering a multivariate analysis including age.

Table 13: Logistic Regression Results for Best Overall Response versus Steady State Exposure (AUC and Cmax) for the Sum of Entrectinib and M5 in Paediatric Patients with NTRK Fusion when Age is Included

Scale	Baseline age	C_{max} at SS for the sum of entrectinib and M5	AUC at SS for the sum of entrectinib and M5
Original	0.0255 (0.761)	-0.000122 (0.637)	-
Original	0.0394 (0.656)	-	-0.0000121 (0.452)
Log10	0.0314 (0.710)	-1.26 (0.477)	-
Log10	0.0450 (0.608)	-	-1.62 (0.355)

AUC = area under the concentration-time curve; C_{max} = maximum concentration; SS = steady state.
Values represent slope (p value).

Table 14: Logistic Regression Results for Best Overall Response versus Steady State Exposure (AUC and Cmax) for the Sum of Entrectinib and M5 in Paediatric Patients with ROS1 Fusion when Age is Included

Scale	Baseline age	C_{max} at SS for the sum of entrectinib and M5	AUC at SS for the sum of entrectinib and M5
Original	-0.0483 (0.715)	0.000520 (0.114)	-
Original	-0.0432 (0.739)	-	0.0000270 (0.151)
Log10	-0.0488 (0.714)	3.80 (0.127)	-
Log10	-0.0443 (0.734)	-	3.32 (0.156)

AUC = area under the concentration-time curve; C_{max} = maximum concentration; SS = steady state.
Values represent slope (p value).

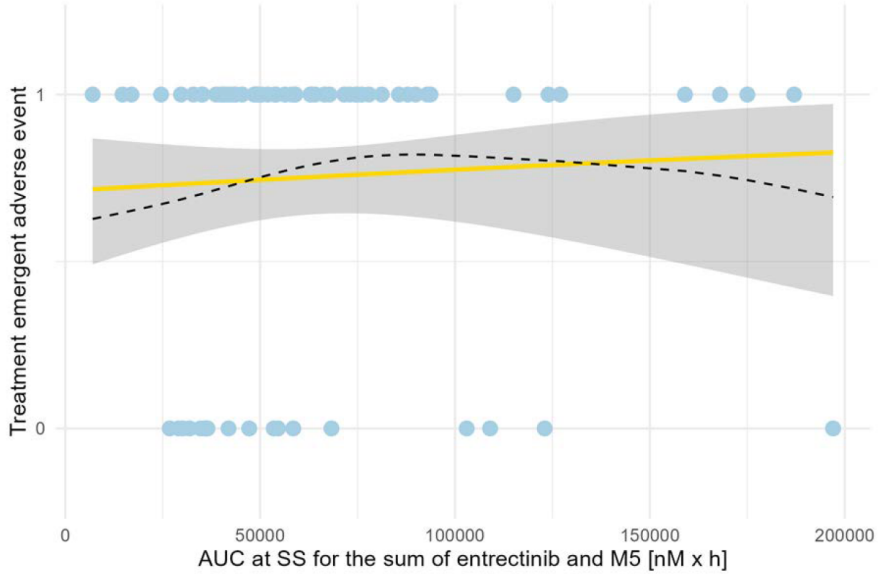
The evaluation of the relationship between exposure of entrectinib and M5 (i.e. their sum) and safety were conducted by analysing data from 73 paediatric patients, with available secondary PK parameters, and available efficacy information. Overall, 55 (75%) reported treatment-emergent AE grade 3 or higher and 34 (47%) experienced a SAE. The logistic regression models (univariate analysis) using exposure metrics (i.e. AUC and Cmax of entrectinib, M5 and their sum on Day or at SS) on normal or log10 scale did not show differences in exposure levels between patients without and with both treatment-emergent AE grade 3 or higher and SAE.

Table 15: Summary Statistics of the Sum of Steady State AUC for Entrectinib and M5 in Paediatric Patients with and without Treatment-Emergent Adverse Events Grade 3 or Higher

Treatment emergent adverse event	N	Mean	SD	P5	Median	P95
No	18	62100	44500	28800	44600	134000
Yes	55	67000	38700	22300	58100	162000

AE, adverse event; AUC, area under the concentration time curve; N, number of patients; nM, nanomolar; h, hour; SD, standard deviation; P5, 5th percentile; P95, 95th percentile.
Source: TF.R

Figure 3: Shape of the Relationship between Treatment-Emergent Adverse Events Grade 3 or Higher and the Sum Of Steady State AUC for Entrectinib and M5 in Paediatric Patients



AE, adverse event; AUC, area under the concentration-time curve, nM, nanomolar; h, hour. Symbols: observed data. Solid yellow line and grey shaded area: smoothed line fitted to the data using a logistic regression and its corresponding 95% confidence interval. Red dashed line: spline fitted to the observed data.
Source: TF.R

Table 16: Logistic Regression Results for Treatment-Emergent AEs grade 3 or Higher versus Exposure in Paediatric Patients when Age is Included

Scale	Analyte	Metrics	Slope exposure (p value)	Slope age (p value)
Original	Entrectinib	C_{max} D1	0.000195 (0.493)	-0.0946 (0.0780)
Original	Entrectinib	C_{max} SS	0.000268 (0.188)	-0.115 (0.0425)
Original	M5	C_{max} D1	-0.0000169 (0.957)	-0.0841 (0.105)
Original	M5	C_{max} SS	-0.00000274 (0.991)	-0.0838 (0.104)
Original	Entrectinib+M5	C_{max} D1	0.0000713 (0.688)	-0.0866 (0.0953)
Original	Entrectinib+M5	C_{max} SS	0.000120 (0.366)	-0.0973 (0.0693)
Original	Entrectinib	AUC D1	0.0000197 (0.322)	-0.105 (0.0590)
Original	Entrectinib	AUC SS	0.0000211 (0.113)	-0.130 (0.0290)
Original	M5	AUC D1	-0.00000176 (0.929)	-0.0842 (0.104)
Original	M5	AUC SS	-0.000000799 (0.954)	-0.0837 (0.104)
Original	Entrectinib+M5	AUC D1	0.00000717 (0.561)	-0.0902 (0.0864)
Original	Entrectinib+M5	AUC SS	0.00000890 (0.285)	-0.104 (0.0578)

Log10	Entrectinib	C_{max} D1	0.931 (0.403)	-0.100 (0.0696)
Log10	Entrectinib	C_{max} SS	1.32 (0.207)	-0.117 (0.0454)
Log10	M5	C_{max} D1	-0.0197 (0.984)	-0.0840 (0.108)
Log10	M5	C_{max} SS	0.459 (0.674)	-0.0828 (0.108)
Log10	Entrectinib+M5	C_{max} D1	0.824 (0.484)	-0.0907 (0.0842)
Log10	Entrectinib+M5	C_{max} SS	1.41 (0.231)	-0.105 (0.0558)
Log10	Entrectinib	AUC D1	0.938 (0.356)	-0.107 (0.0635)
Log10	Entrectinib	AUC SS	1.13 (0.213)	-0.120 (0.0451)
Log10	M5	AUC D1	0.0891 (0.929)	-0.0832 (0.109)
Log10	M5	AUC SS	0.551 (0.600)	-0.0841 (0.103)
Log10	Entrectinib+M5	AUC D1	0.997 (0.383)	-0.0956 (0.0738)
Log10	Entrectinib+M5	AUC SS	1.34 (0.208)	-0.109 (0.0506)

AUC = area under the concentration-time curve; C_{max} = maximum concentration; D1 = Day 1; SS = steady state.
Values represent slope (p value).

Table 17: Logistic Regression Results for Treatment-Emergent Serious AEs grade 3 or Higher versus Exposure in Paediatric Patients when Age is Included

Scale	Analyte	Metrics	Slope exposure (p value)	Slope age (p value)
Original	Entrectinib	C_{max} D1	0.0000448 (0.873)	-0.176 (0.00274)
Original	Entrectinib	C_{max} SS	0.0000796 (0.651)	-0.183 (0.00288)
Original	M5	C_{max} D1	-0.000196 (0.538)	-0.179 (0.00205)
Original	M5	C_{max} SS	-0.0000885 (0.711)	-0.175 (0.00231)
Original	Entrectinib+M5	C_{max} D1	-0.0000418 (0.794)	-0.173 (0.00252)
Original	Entrectinib+M5	C_{max} SS	0.0000126 (0.912)	-0.175 (0.00278)
Original	Entrectinib	AUC D1	0.00000989 (0.589)	-0.185 (0.00267)
Original	Entrectinib	AUC SS	0.00000543 (0.574)	-0.189 (0.00312)
Original	M5	AUC D1	-0.00000893 (0.649)	-0.177 (0.00222)
Original	M5	AUC SS	-0.00000281 (0.841)	-0.174 (0.00242)
Original	Entrectinib+M5	AUC D1	0.000000548 (0.960)	-0.174 (0.00263)
Original	Entrectinib+M5	AUC SS	0.00000204 (0.763)	-0.179 (0.00302)

Log10	Entrectinib	C_{max} D1	0.529 (0.590)	-0.182 (0.00233)
Log10	Entrectinib	C_{max} SS	0.754 (0.424)	-0.193 (0.00231)
Log10	M5	C_{max} D1	0.141 (0.871)	-0.172 (0.00336)
Log10	M5	C_{max} SS	0.486 (0.610)	-0.171 (0.00292)
Log10	Entrectinib+M5	C_{max} D1	0.409 (0.692)	-0.175 (0.00233)
Log10	Entrectinib+M5	C_{max} SS	0.788 (0.456)	-0.184 (0.00203)
Log10	Entrectinib	AUC D1	0.661 (0.502)	-0.190 (0.00262)
Log10	Entrectinib	AUC SS	0.763 (0.392)	-0.201 (0.00277)
Log10	M5	AUC D1	0.344 (0.702)	-0.170 (0.00345)
Log10	M5	AUC SS	0.696 (0.471)	-0.174 (0.00260)
Log10	Entrectinib+M5	AUC D1	0.700 (0.520)	-0.180 (0.00212)
Log10	Entrectinib+M5	AUC SS	1.00 (0.347)	-0.194 (0.00188)

AUC = area under the concentration-time curve; C_{max} = maximum concentration; D1 = Day 1; SS = steady state.
Values represent slope (p value).

Bone fractures

Exposure-response analysis was performed using data from 73 paediatric patients, out of which 18 (25%) experienced at least one mild to severe bone fracture (Grade 1 to 3). The median time to first bone fracture was 190 days (range: 63-871 days). In the exploratory analysis, patients with bone fracture were found to have a larger median average entrectinib concentration up to the time of first event (Cav,event, 2070 nM) compared to patients without event (median of 1420 nM). Despite a large overlap in Cav,event between the two populations, this trend was further confirmed by the univariate logistic regression analysis, which identified that the probability of bone fracture was increasing when entrectinib Cav,event increases. The log-odds of bone fracture was increased by ~6% for every 100 nM increase in the predicted Cav,event. Contrary to entrectinib, larger M5 concentrations were not associated with a higher risk of bone fracture.

Table 18: Univariate logistic regression results for the occurrence of bone fracture versus exposure in Paediatric patients

Scale	Analyte	Metrics	Slope (p value)
Original	Entrectinib	$C_{av,event}$	0.000636 (0.018)
Original	M5	$C_{av,event}$	0.00000968 (0.978)
Original	Entrectinib+M5	$C_{av,event}$	0.000266 (0.12)
Log10	Entrectinib	$C_{av,event}$	1.10 (0.017)
Log10	M5	$C_{av,event}$	0.30 (0.488)
Log10	Entrectinib+M5	$C_{av,event}$	0.919 (0.068)

$C_{av,event}$, average concentration up to the time of the first bone fracture or censoring. On the original scale, slope have units of nM.
Source: /_Projects/RO7102122_Solid tumor_30226/PopPK/TTE-BF/Step 76/distribution-exposure-bf.html

Additional logistic regression analyses were performed to evaluate the relationships between other exposure measures (other than Cave) and the occurrence of bone fracture event. Results from the univariate logistic regression models demonstrated a significant correlation between the entrectinib AUCss and the incidence of bone fractures. (This correlation was statistically significant on both the normal and log10 scales). The steady-state maximum concentration (Cmaxss) of entrectinib was not associated with the risk of bone fractures on either of the scales and in addition, AUCss and Cmaxss of either M5 or the sum of entrectinib and M5 did not show a significant correlation on either scale.

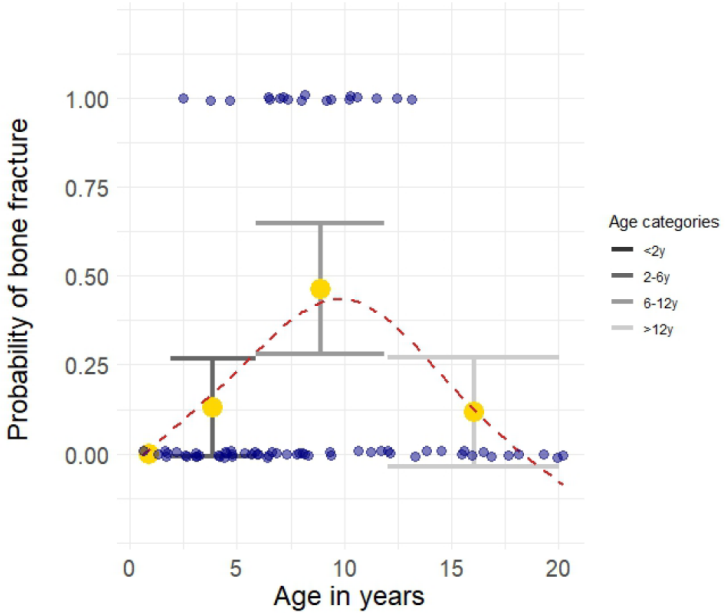
Table 19: Results from the Univariate Logistic Regression for occurrence of bone fracture versus steady state exposure of entrectinib, M5 or their sum

Scale	Analyte	Metrics	Slope exposure	p value
Original	Entrectinib	$C_{max,ss}$	0.000241	0.098
Original	M5	$C_{max,ss}$	-0.00029	0.310
Original	Entrectinib+M5	$C_{max,ss}$	7.84E-05	0.446
Original	Entrectinib	$AUC_{,ss}$	1.76E-05	0.043
Original	M5	$AUC_{,ss}$	-9.9E-06	0.510
Original	Entrectinib+M5	$AUC_{,ss}$	7.2E-06	0.243
Log10	Entrectinib	$C_{max,ss}$	0.6091	0.117
Log10	M5	$C_{max,ss}$	-0.3622	0.404
Log10	Entrectinib+M5	$C_{max,ss}$	0.3525	0.428
Log10	Entrectinib	$AUC_{,ss}$	0.7099	0.043
Log10	M5	$AUC_{,ss}$	-0.1365	0.742
Log10	Entrectinib+M5	$AUC_{,ss}$	0.5419	0.200

AUC = area under the concentration-time curve; C_{max} = maximum concentration; SS = steady state.

Age was found as predictor of bone fractures when categorized into four categories (<2y, 2-6y, 6-12y and >12y; Figure below; p-value = 0.005). The highest probability of bone fracture was identified for ages between 6-12 years.

Figure 4: Logistic regression for the occurrence of bone fracture versus age categories



Age categories were defined as <2y, 2-6y, 6-12y and >12y of age. Blue symbols represent the data. Predicted probabilities for each age group using a logistic regression are represented by error bars (95% prediction interval) around the observed mean probability (yellow symbols). Red dashed line represent a spline fitted to the observed data.
Source: /_Projects/RO7102122_Solid tumor_30226/PopPK/TTE-BF/Step 76/distribution-exposure-bf.html

A multivariate logistic regression model including age (as categories) and entrectinib exposure as predictors showed that the effect of entrectinib exposure was less pronounced (p-value > 0.05) when age was included as a predictor of bone fracture. Moreover, addition of entrectinib to the model including age categories as predictor did not further improve model fit.

2.5.3. Discussion on clinical pharmacology

Formulations

F06 oral suspension

In the current variation a new route of administration of F06 capsule is proposed for patients able to swallow liquids or patients who require enteral administration. The capsule formulation (F06) may be prepared as an oral suspension and administered via oral syringe or gastric/nasogastric tube. This method and route of administration are currently used in Study CO40778 (STARTRK-NG) and Study BO41932 (TAPISTRY). A relative bioavailability study (GP44192) was conducted with the capsule suspensions in healthy adults to support administration of the oral suspension (via nasogastric route or with a syringe), and the effects of co-administration of lansoprazole, a proton pump inhibitor (PPI). This study also aimed to assess the palatability of both oral suspensions in water and milk.

Information on step followed to prepare the suspension is not present in the protocol, but it is of note that, in the Study GP44192 the suspension is made suspending 600 mg in 30 ml of water or milk and the entire suspension was administered.

Based on results from study GP44192, the relative bioavailability is demonstrated for the NG suspension as well as for the oral suspension in water versus the reference F06 whole capsules, with a 19% lower Cmax for the oral suspension in water that can be considered negligible.
A higher Cmax (24%) is instead showed for the oral suspension in milk versus the whole capsules, however the AUCinf is only 13% higher
A logistic regression analysis to assess the impact of the increased exposure of 14% AUC with the oral suspension in milk on the probability of increase occurrence of bone fractures respect to that expected for patients receiving the F06 whole capsules was provided. Based on this analysis the probability of bone fractures in case of the expected increase of exposure with the suspension in milk ranged from 0.4% to 1.6% across the age categories considered (1-6 months, 6 months-0.5 m2 and 0.51-0.80 m2). Since the AUC is the PK parameter to be considered to assess an impact on safety, this logistic regression analysis showed that the probability of an increase of bone fractions is negligible in case of administration of suspension in milk.
Therefore, from a PK point of view the oral/NG suspension in water or milk showed entrectinib exposure similar to that reached with the whole F06 capsules.

Regarding the palatability, although it cannot be excluded that the acceptability observed in this study conducted in adult patients can be extrapolated to the children, results do not reveal major problems.

Coated granules

In Study GP41341 F15 and F16 granules formulations (containing the same Form A but a different coating) were compared to the approved F06 capsule formulation (Form C).

The proposed commercial coated granule formulation (**F17**) contains entrectinib polymorphic Form C (only three subjects in STARTRK-NG were dosed with F17).

Study GP41341 assessed rBA between F15 granules and F06 capsule. Variability was similar for both F15 and the F06 capsule formulation. However, the CV% for AUC0-inf and Cmax following administration of a single dose of entrectinib considered for the calculation of samples size was 20% and 16%, respectively. Although the sample size could be underestimated considering the variability found within the study, the GMR and CI are within the BE criteria.

Entrectinib and M5 exposures were examined separately, but since M5 is pharmacology active, the active moiety should have been assessed. As the BE has been shown for the two separate moieties this is not considered an issue. Entrectinib PK parameters were comparable between F15 and F06 formulation following administration of a single oral dose of 600 mg entrectinib with a light meal.

F16 showed a 90%CI for AUC0-t outside the BE margins, however, this formulation is not proposed for approval.

The relative bioavailability study GP41341 was conducted in fed condition in order to match dosing instructions for paediatric patients in the ongoing clinical trial (STARTRK-NG), which recommends administration of entrectinib with a meal for the initial F1 formulation.

In study STARTRK-NG, other formulations were introduced, where F06 was to be given without specific food intake recommendations as well as the granules F15 that, as per protocol, can be taken with soft food or, additionally, only with water.

A Virtual BE (report 1113585, that was an extension of a previously described physiologically based pharmacokinetic model) was submitted with the aim to support extrapolation of fed state bioequivalence to fasted state. The PBPK report has been extensively revised during the procedure and although its quality significantly improved, uncertainties remain due to the fact that the predictions of key PK indices do not match the observed results. The proposed model was then considered not fit for purpose. However, due to the lack of food effect on capsules, the BE demonstrated between F15 granules and F06 capsules, the need to administer the granules with soft food, although the amount of food might be small, strict fast will not be applied, therefore concluding that no restriction regarding food can be applied.

It is of note that F15 and F06 used in this rBA study contains the polymorph A and not the polymorph C of the commercial formulation (F17). There is no relative bioavailability study conducted between coated granules (F15 Form A) and coated granules (F17 Form C).

Considering that the BE between F15 (Form A) and F06 (Form A) has been demonstrated, the solubility and in vitro dissolution profile of the two polymorphs A and C in the drug substance has been considered acceptable during the IMA, the BE has been demonstrated during the IMA between F06 (Form C) and F06 (Form A) and the comparable dissolution profile between F15 (Form A) and F17 (Form C), the waiver of the in vivo study with F15 and F17 is considered acceptable.

The palatability questionnaire was administered to subjects included in the Part 1 of Study GP41341. Overall, no major differences were noted between the two formulations F15 and F16. The granules formulation is intended for patients unable to swallow capsules, but able to swallow soft food; the intended age is from 6 months and above and for this age range the proposed dose recommendation is 300 mg/m2 with a maximum of 600 mg for children with BSA ≥1.51 m2. The dose to be administered to these patients ranged from 100 mg to 600 mg, therefore the number of granules ranges from 40 to 240. The Applicant refers to a figure in Module 3 in which it can be noted that the number of coated granules of the 300 mg dose (120 granules) correspond to less than half of tablespoon. Doses higher than 300 mg are foreseen for adolescent patients and above for which the capsules are available, but, in any case, the number of granules to be administered does not represent an issue.

It is unknown how the administration can be managed if granules were inadvertently chewed, taken into account the bitter taste of entrectinib.

The administration of coated granules with soft food reduced the risk of chewing and that only one six-years old patient tried to chew granules, but was trained to avoid it and the administration continued for 5 months. It is acknowledged that no evaluation can be performed with this data on the effect of chew the granules PK. However, as the coating of granules is not functional and the granules disintegrate in few minutes, the effect of chewing on PK is expected to be negligible.

Regarding the possibility to partially spit/vomit the granules, the SmPC/PL has been amended in order to instruct patients/caregivers to refer to the HCP.

Dose recommendation

Within this variation, new PK analysis in children, adolescents, and young adult patients were performed with new data from the updated Study CO40778 (STARTRK-NG) pooled with data from previous studies; Study GO40782 (STARTRK-2; RXDX-101-02) and Study BO41932 (TAPISTRY).

The main amount of PK data is derived from STARTRK-NG study (about 60 patients treated with different doses and formulation/route of administration), in addition PK data are available from two paediatric patients enrolled in Study GO40782 (STARTRK-2; RXDX-101-02) and from four paediatric patients enrolled in study BO41932 (TAPISTRY).

Non-compartmental analysis was performed at Cycle 1 day 1 (after single dose) and Cycle 2 day 1 (steady state). It is observed that all patients taking F06 suspension through NG administration showed lower exposure with respect to patients taking F06 whole capsules. In addition, lower exposures have also been observed in patients below 1 year taking granules formulations that is not so evident in older patients (>1 year).

The proposed dose recommendations derived from modelling and simulation analysis obtained from PBPK model (Gastroplus 1091111 and Symcyp 1091399), updated popPK model 1121816 and updated PBPK 1119857. Gastroplus 1091111 and Symcyp 1091399 models were already submitted within the IMAA and were considered not satisfactory for their intended purposes due to the lack of a full and reliable qualification/validation and also its limited simulation properties making them inadequate to provide data to support dose recommendation.

The updated PBPK model (Simcyp, Report 1119857) submitted with the paediatric application was used to propose dose adjustment recommendations when entrectinib is co-administered with CYP3A4 inhibitors.

Patients < 1 month

The proposed dose in neonates from birth to < 1 month of age was based on previous Simcyp and GastroPlus PBPK models (Report 1096959 and Report 1091111, respectively), although as already remarked during the assessment of the initial MA, the two models were not deemed to be satisfactory to be used for prediction of exposure and to substitute actual observations in this age group. The PBPK models do not fulfil the requirements for qualification, model assumptions have not been discussed and justified and no update to these models has been submitted within this application. In addition, no neonates from birth to 1 month have been recruited in any of the clinical studies (CO40778 [STARTRK-NG] and BO41932 [TAPISTRY]).

Also, despite the prediction for the sum of entrectinib + M5 for patients <1 month of age partially fall within the range of the observed sum for paediatric patients with the age range >1 month to < 1 years, the 5^{th}-95^{th} percentiles intervals of predicted exposures were too wide (a very wide range of observed values can fall within that interval). In addition, it was observed that the model mis-predicts entrectinib and M5 exposures (overpredicting and underpredicting systemic exposures of entrectinib and M5, respectively), in the group aged ≤2 years old. Overall, there was an unexplained age effect on the bioavailability of entrectinib probably due to the inadequacy of the PBPK model to correctly take into account some aspects/variables, like for example changes in gastric pH in younger children, and then the uncertainties mainly related to many gaps in understanding the physiological changes in very young children still remains and make the PBPK models are inadequate for the intended purpose.

All the above considered, the CHMP conclusion is that proposed dosage for patients 1 month or less is not agreeable and cannot provide sound evidence for a recommendation of indication in this age range. In addition, no supporting clinical data are available to confirm the proposed recommended dosage in newborns

to patients below 1 month of age. As a consequence, the indication was amended to exclude patients below or equal than 1 month of age.

Patients ≥1 month to ≤ 6 months of age

The dose selection in this age range was initially based on the updated PopPK analysis, and observed PK data were available from only 5 patients below 6 months of age and treated with NG suspension, with a response rate of 4/5. Observed PK data in these patients show lower exposure compared to that reached with the whole capsule F06 in adults and older children, for two of them, the steady state exposure was below the lower limit of CI95 of simulated adult steady state exposure, one had a PR and one SD. Among several possible explanations of this lower exposure, the MAH considered the higher M/P ratio observed in smaller children. However, a highly variable M/P ratio among the considered patients (taking F06 NG formulation) precludes generalization from this finding. In addition, data show that the M/P-ratio is not constant across age, and also that there is a large variability in that value when comparing different formulations.

Also, the additional data provided by the MAH show that PBPK model used to select dose in this age range was considered to have limited simulation properties and is therefore inadequate to support dosing recommendations in younger children.

Observed PK data are very limited and biased by several uncertainties providing only a minor supportive evidence for dose recommendation. However, the positive benefit risk balance in this population is derived mostly from clinical evidence: the antitumor activity shown by entrectinib in the age range 0-6 months (6/7 responders) does not support an exclusion of younger children (<6 months) from entrectinib indication. From a safety perspective, SAEs were higher in this range as compared to older age ranges (>2 years), a specific pattern in distribution of the most relevant ADRs is not noted. Hence, the safety profile in this age range is considered acceptable.

Therefore, dosage recommendations should be mainly derived from the observed benefit and risk at the dose used in the clinical trial for this population.

Patients ≥ 6 months of age

PK data in this age range were initially submitted based on the three BSA categories foreseen in the posology. BSA I (covering patients from 6 months to about one year), BSA II (including patients >1.4 years-6.3 years) and BSA III (including patients from 5.12 years to 11 years).

Observed PK data in BSA I category were available at Day 1 for 3 children taking granules and for 7 children at steady state after switching from other formulations. Exposures for the 3 children at Day 1 seemed lower than those observed in older children taking other formulations, while seemed comparable for the 7 children at steady-state.

According to the updated PopPK report, simulated exposures in children with BSA I were 30% of that in adults.

Observed PK data in BSA II category seemed to be more in line with those reached in older children and adults, however this BSA category was considered too wide and the MAH was suggested to split it in two sub-categories to allow a more accurate prediction of exposure.

Therefore, the initial BSA category II (0.51-0.80 m^2) was split into two categories: category IIa (0.51-0.65 m^2) and category IIb (0.66-0.80 m^2). Two set of simulations were performed using the final popPK model for a virtual population of 25000 paediatric patients using the same methodology as presented in the popPK report submitted in the paediatric application (Report 1121816). In the first one, a dose of 200 mg QD was

assumed for both BSA categories IIa and IIb while in the second one, a dose of 150 mg QD was assumed for category IIa and of 200 mg QD for category IIb. Results for these two sets of simulation showed that that 150 mg for BSA category IIa would result in exposure 25% lower respect to 200 mg, but probably 250 mg in category IIb would give an exposure more in line with that in adults. Overall, the validity of the proposed BSA categories was considered inadequate as the application of the popPK models led to inaccurate exposures predictions through the simulations in the current category I and II.

In particular, additional pcVPCs stratified by age, body weight and formulation were provided by the MAH. Briefly, biased and acceptable simulation properties of the popPK model for patients younger than 6 years and older than 6 years were demonstrated, respectively. In particular, in patients younger than 0.5 years (N=6), the popPK model under-predicts the concentrations of entrectinib and M5 at early time points (up to 6 h post-dose, Day 1). In patients aged 0.5-6 years, the model tends to slightly under-predict the median entrectinib and M5 concentrations up to ~4 h post-dose (Day 1).
Furthermore, biased and acceptable simulation properties of the popPK model for patients weighting less than 20 kg and more than 20 kg were demonstrated, respectively. In particular, in patients weighing less than 10 kg, a bias has been observed at early time points (0-6 h post-dose) where the model under-predicts the concentrations of M5, and to a lesser extent of entrectinib. In patients weighing 10-20 kg, the model tends to slightly under-predict the entrectinib and M5 concentrations at early time points (1-2 h post-dose).
To explain the observed biases, the MAH argues that a higher M/P ratio was observed in younger than in older children. These differences could be a consequence of physiological differences (e.g. different plasma protein levels) between the different age groups, which are not captured by the empirical popPK model. In addition, the MAH states that, notwithstanding the limitations of the model, the clinical evidence collected on efficacy supports the choice of dose in the lower age groups. Given the uncertainties highlighted by these additional analyses, the popPK model appears inadequate for its intended purpose. At present, the doses recommended in the lower categories (less than 6 years of age, BSA categories I and II) are supported by the clinical evidence of efficacy and safety collected in a limited number of patients.

Efficacy (in relation to the NTRK indication), although in a limited dataset of patients, demonstrated a quite consistent ORR response across age groups and also with that reported in a larger data set of adults/adolescents. In addition, although numbers are limited in the different age groups and hence sound conclusions could not be made, the safety data across ages do not highlight a specific trend in ADRs occurrence [fractures in patients aged 6-12 years and infections in the lowest age ranges (0-6 months, 6 months-2 years)]. In these lower age groups a higher frequency of SAEs, mainly related to infections, is reported.

For paediatric patients >6 month of age in the BSA category I (0.43–0.5 m^2) a flat dose approach (100 mg) was used in the clinical trial. It is estimated to translate into an equivalent BSA-based dose range of 200-233 mg/m^2. Despite representing a potential lower dose than paediatric patients aged 1 month - 6 months, who received a BSA-based dose of 250 mg/m^2, the 100mg flat dose was deemed the most appropriate as being in line with the clinical trial data and considering that revised BSA based doses proposed by the MAH (300 mg/m2) could lead to an increase into exposure at steady state (AUCss) and the associated probability of bone fracture. Indeed, compared to the 100 mg flat dose, the AUCss of entrectinib increased by 13% and 34% for the doses of 250 and 300 mg/m2 and respectively these increases in entrectinib exposure translate in a small increase in the risk of bone fracture from 13.1% (100 mg) to 13.6% (250 mg) and 14.4% (300 mg).

Although the increase in bone fractures risk is relatively small, it is of note that the shift from 100 mg flat to 300 mg/m2 in the BSA category I improves matching with exposures in older children only in a negligibly way and the exposure in children below 6 months and dosed with 250 mg/m2 is much lower.

Further analysis regarding the predictive properties of the popPK models give rise to further doubts. Indeed, they show that the exposures predicted through the simulations in the current category I and II are affected by error due to the inaccurate predictions obtained through the application of the popPK models that make uncertain also the predict percentage of increase in exposure (+34%) moving patients in BSA category I from 100 mg to dose closer to 300 mg/m2 and the related estimated increment in associated risk of bone fracture.

Based on these considerations, the flat dose of 100 mg was reinstated.

Moreover, in order to avoid that patients ≥6 months and below the lower BSA limit (0.43) not have any dosing recommendation and considering that the flat dose of 100 mg in these patients could expose them to higher mg/m2 dose than that in patients with BSA category I, a possibility to use 250 mg/m2 dose for patient ≥6 months and BSA ≤ 0.42 has been introduced in the SmPC section 4.2 table 1.

The recommended doses per BSA categories are as follow:

Body surface area (BSA)*	Once daily dose
≤ 0.42 m^2	250 mg/m^2
0.43 m^2 to 0.50 m^2	100 mg
0.51 m^2 to 0.80 m^2	200 mg
0.81 m^2 to 1.10 m^2	300 mg
1.11 m^2 to 1.50 m^2	400 mg
≥ 1.51 m^2	600 mg

Recommendations for dose reduction due to tolerability

The proposed dose reduction as reported in the SmPC is the following:

Starting dose once daily	First dose reduction	Second dose reduction	Permanently discontinue Rozlytrek in patients who are unable to tolerate Rozlytrek after two dose reductions.
250 mg/m^2	Reduce the once daily dose to two thirds of the starting dose*	Reduce the once daily dose to one third of the starting dose*	
100 mg	50 mg or 100 mg once daily, according to schedule**	50 mg once daily	
200 mg	150 mg once daily	100 mg once daily	

300 mg	200 mg once daily	100 mg once daily	
400 mg	300 mg once daily	200 mg once daily	
600 mg	400 mg once daily	200 mg once daily	
*To enable dosing increments of 10 mg, capsules prepared as an oral suspension may be used. Refer to the Method of administration section below and section 6.6. **Monday (100 mg), Tuesday (50 mg), Wednesday (100 mg), Thursday (50 mg), Friday (100 mg), Saturday (50 mg), and Sunday (100 mg).			

The dose reduction algorithm in the paediatric population is substantially based on the traditional dose reduction algorithm of 33% in the oncology setting and simulations with the updated popPK were performed to estimate how comparable the system exposure was to the adult population dose reduction algorithm.

Drug Drug Interaction

No dedicated DDI studies have been performed in children. The in vitro Study 1116011 confirms information already reported in the SmPC.

A PBPK model has been performed with the aim to predict the exposure changes of entrectinib and its major circulating and equally potent metabolite, M5, after multiple oral administration of entrectinib in paediatrics in the presence of either moderate or strong CYP3A4 inhibition.

Poor estimation of the steady-state systemic exposure of entrectinib and M5 for children < 2 years was identified when comparing PBPK model predictions of dose-normalized AUC(0-t) and Cmax to those estimated from clinical observations. Given the magnitude of the miss-prediction, no victim DDI simulations was done. Therefore, no dose recommendation for entrectinib with DDI effects of CYP3A4 perpetrators can be justified for this age group.

According to the updated PBPK models, the predicted median AUC(0-t) and Cmax values of entrectinib and M5 at the last dose after multiple (steady-state) oral administrations of entrectinib in adults and children (≥ 2 years of age) are comparable to the respective clinical observations. However: a) the observed PK data in the BSA categories IIa – V were obtained from only 43 (entrectinib) and 42 (M5) individuals, compared to a larger (more than 200 subjects) cohort of adults, b) it is not mentioned which formulations (one or more) were administered, and c) the predicted and observed min and max values are not comparable in some age groups. Therefore, the credibility of the latest PBPK models in terms of their ability to accurately estimate the steady-state systemic exposure of entrectinib and M5 in paediatric patients remains uncertain. In addition, due to the variability of the predicted DDI data, the exposure changes of entrectinib and M5 following oral administration of entrectinib in paediatric patients above and equal to 2 years old in the presence of either moderate or strong CYP3A4 inhibition are largely uncertain. Finally, dose-linear PK of entrectinib in paediatric patients is difficult to be assessed and demonstrated given: a) the limited number of patients; b) that systemic exposure following repeat dosing administration appeared to increase in a supra-proportional manner from 400 mg/m^2 to 550 mg/m^2 (Meneses-Lorente G. et al., 2023). Therefore, the concomitant use CYP3A4 inhibitors in paediatric patients above and equal to 2 years old should be avoided**.** This is particularly relevant as a significant relationship between exposure to entrectinib and occurrence of bone fracture in paediatric patients (see Report No. 1121816) has been established. Thus, the proposed dose

recommendation for entrectinib with DDI effects of either strong or moderate CYP3A4 perpetrator in paediatric populations are not justified and not included in the SmPC.

In the protocol study for STARTRK-NG it is reported that: "moderate inducers of CYP3A, CYP3A4, or CYP3A4/5, such as dexamethasone or other glucocorticoids, may be used at the discretion of the Investigator" and 30.9% of patients required dexamethasone administration.

Although PK profile seems to be not affected by coadministration of dexamethasone, probably a table with observed exposures would have been useful. Dexamethasone used at low doses can be defined a weak CYP3A4 inducers, however, it is not clear at what dosage the drug has been used in the reported patients, neither if a higher dosage could cause a significant induction of CYP3A4 and thus determine a decrease in the entrectinib exposures.
The SmPC section 4.5 has been amended in order to add dexamethasone in the list of CYP3A/P-gp inducers to be avoided.
Since patients with CNS tumour can benefit from dexamethasone therapy as demonstrated by the percentage requiring its administration in Study STARTRK-NG, a wording in SmPC has been added to inform that if co-administration of Rozlytrek with dexamethasone cannot be avoided, dexamethasone dose recommendations should be determined by the healthcare professional.

Pharmacodynamic

The PopPK analysis 1121816 aimed to characterize the relationship between exposure of active moieties (entrectinib and M5), and efficacy outcome (responder status based on best overall response [BOR]) and safety outcomes (treatment-emergent adverse events [AEs] of grade 3 or higher, serious adverse events [SAEs], and bone fractures).

In the Exposure-response analysis, the logistic regression models (univariate analysis) using exposure metrics (i.e. AUC and Cmax of entrectinib, M5 and their sum at SS) on normal or log10 scale did not show differences between responders and non-responders both in the NTRK and ROS1 group, although this was not so evident in the ROS1 group where a trend in E-R correlation was observed but the limited number in each group (Yes, No) was small to draw clear conclusions. Results from the multivariate logistic regression analyses evaluating the relationship between the sum of entrectinib and M5 steady state exposure (Cmax or AUC, either on the original or log10 scale) and best overall response when age was included in the model have been presented for both NTRK fusion-positive paediatric patients and for ROS1 fusion-positive patients. Upon inclusion of age in the logistic regression models, none of the exposure-response relationship was statistically significant. These additional analyses confirm that the between-patient variability in exposure does not explain the variability in response, and that the previous conclusion on the lack of an exposure-response relationship remain the same when considering a multivariate analysis including age.

. The Exposure-safety analysis indicated that higher exposure levels in the exposure range studied were not associated with a higher occurrence of treatment-emergent AEs grade 3 or higher and SAEs. However, as for the efficacy these conclusions remain uncertain given the limited sample size.

In order to better understand the between-patient variability in exposure-response relationship (safety), results from the multivariate logistic regression analyses including age confirm that the between-patient variability in exposure does not explain the variability in safety, and that the previous conclusion on the lack of an exposure-safety relationship remain the same.

Bone fractures

On the basis of safety data related to bone fractures available until now, the probability of bone fracture between male and female subgroups seems to be similar.

The current available data do not allow disentangling the contribution of entrectinib and the contribution of age on the risk of bone fracture. However, under the assumption that only entrectinib exposure is influencing the risk of bone fracture in the paediatric population, then the risk of bone fracture was found to increase from 13% to 41% between the low and high quartiles of entrectinib average concentration in the studied population.

No information is available on the impact on PK parameters in case the oral suspension is spitted out. As reported in the SmPC/PL, in case of vomiting occurs immediately after taking a dose of ROZLYTREK (capsule whole or granules), the dose should be repeated. In case of total vomiting/spitting of oral suspension, the SmPC/PL has been amended in order to instruct patients/caregivers to refer to the HCP.

2.5.4. Conclusions on clinical pharmacology

The pharmacology data in patients 1 month or less cannot provide sound evidence for a recommendation of indication in this age range .

Regarding patient from 1 month to < 6 months, the additional provided data show that PBPK models have limited simulation properties and are therefore inadequate to provide data to support dosing recommendations in younger children. Therefore, dosage recommendations should be mainly derived from the benefit-to-risk assessment in this population.

For patients above 6 months, the recommended doses in the lower BSA categories I and II (0.43 m2 to 0.50 m2; 0.51 m2 to 0.80 m2) are supported by the clinical evidence of efficacy and safety collected in a limited number of patients, due to low predictive performance of the PopPK model.

The initial proposed flat dose of 100 mg was considered more adequate than a BSA based dose for patients in BSA category I.

A possibility to use 250 mg/m2 dose for patient >6 months and BSA ≤ 0.42 has been introduced in the SmPC section 4.2 table 1.

2.5.5. Clinical efficacy

To support the two site and histology independent indications for paediatric patients in NTRK fusion positive solid tumours (from birth to 12 years) and in ROS1 fusion positive solid tumours (from birth to 18 years) with no satisfactory treatment options, the MAH submitted **two pooled analyses**, updated during the procedure. The latest datasets include **44 paediatric patients for the NTRK indication** and **19 paediatric patients for the ROS1 indication**, respectively, pooled across 3 clinical trials, **STARTRK-NG (main study)**, **STARTRK-2** and **TAPISTRY (supportive studies).**

Thus, the results supporting efficacy are described in section 3.3.4.6 "Analysis performed across trials (pooled analyses and meta-analysis)"

Table 20: Overview of studies contributing to the efficacy dossier

Study Number	Study Design and Patient Population	Dose	Primary Endpoints	Scope of Safety Data Collection	No. of Patients in Integrated Analyses	Data Cut-off Date
Pivotal Study						
STARTRK-NG (CO40778)	Study Design: Phase I/II open-label, dose escalation, and expansion Population: Paediatric patients with locally advanced or metastatic solid or primary CNS tumours.	**Phase I:** from 250 to 750 mg/m2/day orally or via NG/gastric tube as appropriate **Phase II:** F06: from 100 to 600 mg PO or from 20 mg to 600 mg as aqueous suspension via NG/ gastric tube or orally via a syringe daily F1: from 300 to 600 mg PO daily Coated granules: from 100 to 600 mg PO daily	BICR-assessed ORR	Drug exposure, adverse events, and laboratory assessment	**Efficacy**: **34 with NTRK fusion positive tumours,** **16 with ROS1 fusion positive tumours** Safety: 68 treated patients	Updated 16 July 2023 (enrolment cutoff date: 16 January 2023)

Supportive Studies						
TAPISTRY (BO41932)	Study Design: Phase II, global, multicenter, open-label Population: Paediatric patients with NTRK or ROS1 fusion-positive tumours	600 mg PO daily for patients with BSA ≥ 1.51 m^2 from 100 to 600 mg PO daily for patients with BSA < 1.51 m^2 F06: 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: from 100 to 600 mg PO daily	BICR-assessed ORR	Drug exposure, adverse events, and laboratory assessment	**Efficacy**: **10 NTRK fusion positive,** **1 ROS1 fusion positive treated patients** Safety: 21 treated patients	Updated 16 July 2023 (enrolment cutoff date: 16 January 2023)
STARTRK-02 (GO40782)	Study Design: Phase II, global, multicenter, open-label Population: Paediatric patients with locally advanced or metastatic solid tumours that harbour ROS1 gene rearrangement [a]	600 mg PO daily	BICR-assessed ORR	Drug exposure, adverse events, and laboratory assessment	**Efficacy**: **2 ROS1 fusion positive treated patients** Safety: 2 ROS1 fusion-positive treated patients	Updated 16 July 2023 (enrolment cutoff date: 16 January 2023)

2.5.5.1. Dose response study

STARTRK-NG is a phase I/II study in paediatric patients which included a dose escalation phase (Part A Phase I). A 3+3 design was followed for dose escalation, up to 4 dose levels were evaluated (250, 400, 550, and 750 mg/m^2). The initial paediatric MTD-based RP2D (550 mg/m2) using F1 capsules for oral or gastric/nasogastric tube use once daily for 28-day cycles was based on results of this dose escalation.

2.5.5.2. Main study

STARTRK-NG - A Phase I/II Open-Label, Dose-Escalation and Expansion Study of Entrectinib (RXDX-101) in Pediatrics with Locally Advanced or Metastatic Solid or Primary CNS Tumors and/or who have No Satisfactory Treatment Options.

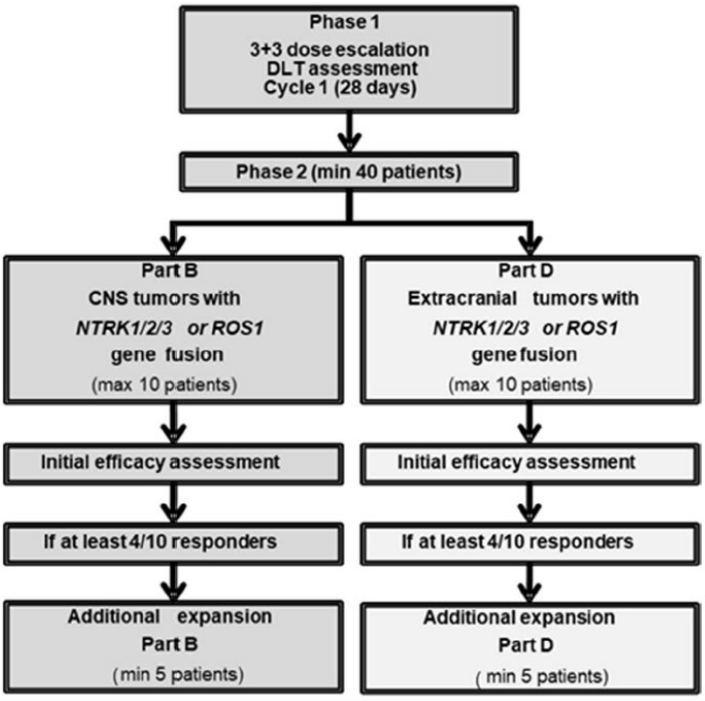
STARTRK-NG was initiated as a dose-escalation study in paediatric patients with relapsed or refractory extracranial solid tumours (Phase I; Part A). The initial study design included 5 expansion cohorts in the

former Phase Ib portion; 3 of the 5 cohorts were closed for the revised Phase II study design and only Cohorts B and D continued to enrol patients (see figure below).

The study is ongoing.

Study was amended 10 times based on accumulating knowledge on entrectinib as well as based on regulatory requests.

Figure 5: updated study design



DLT = dose-limiting toxicity; max = maximum; min = minimum.

Methods

- **Study Participants**

- **Cohort B** (primary brain tumours with gene fusions expansion cohort) to evaluate intracranial tumour response (per RANO) in paediatric patients from birth to < 18 years of age with primary CNS tumours harbouring NTRK1/2/3 or ROS1 gene fusions who have either progressed following prior therapies or who have no acceptable standard therapy.

- **Cohort D** (extracranial tumours with gene fusions expansion cohort) to evaluate tumour response (per RECIST, Version 1.1) in paediatric patients from birth to < 18 years of age with extracranial solid tumours harbouring NTRK1/2/3 or ROS1 gene fusions who have either progressed following prior therapies or who have no acceptable standard therapy.

All patients were male or female <18 years of age, with locally advanced or metastatic disease, or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options for solid tumours and primary CNS tumours that are NTRK or ROS1 gene fusion-positive but no prior treatment with TRK or ROS1 inhibitor, Lansky or Karnofsky performance score ≥60% and minimum life expectancy of at least 4 weeks, adequate organs function.

- **Treatments**

Several formulations of entrectinib were used throughout the study (i.e., F1, F06, and coated granules).

The initial paediatric MTD-based RP2D (550 mg/m2) using F1 capsules was based on the dose escalation part of STARTRK-NG. Based on matching paediatric entrectinib exposures to adult exposures at 600 mg QD (the recommended dose in adults), a dose of 300 mg/m^2, using the capsule formulation (F06), was recommended for paediatric patients aged ≥6 months who can swallow capsules.

Table 21: Recommended F06 Dose for Paediatric patients ≥ 6 months

Category	BSA (m^2)	Once Daily Dose
I	0.43–0.50 m^2	100 mg
II	0.51–0.80 m^2	200 mg
III	0.81–1.10 m^2	300 mg
IV	1.11–1.50 m^2	400 mg
V = Adult	≥ 1.51 m^2	600 mg

Table 22: Recommended Coated Granules for Paediatric Patients ≥ 6 months

Category	BSA (m^2)	Once Daily Dose
I	0.43–0.45 m^2	100 mg (2 × 50 mg)
IIa	0.46–0.60 m^2	150 mg (3 × 50 mg)
IIb	0.61–0.80 m^2	200 mg (4 × 50 mg)
III	0.81–1.10 m^2	300 mg (6 × 50 mg)
IV	1.11–1.50 m^2	400 mg (8 × 50 mg)
V = Adult	≥ 1.51 m^2	600 mg (12 × 50 mg)

BSA = body surface area.

Entrectinib was administered until clinical, laboratory or radiographic evidence of PD, development of unacceptable toxicity, or discontinuation at the discretion of patient/parent/guardian or investigator.

All patients had tumour assessments at screening and every 8 weeks, starting at the end of Cycle 2 (1 cycle=4 weeks). After Cycle 18, disease evaluation was performed every 3 cycles.

- **Objectives**

Primary objectives of STARTRK-NG were to determine/confirm the MTD/RP2D, and to evaluate efficacy in the phase II dose expansion in terms of overall response rate (ORR).

Secondary objectives were to describe safety, PK, to assess efficacy (ORR, DOR, TTR, CBR, OS) in subsets of patients, to describe growth, puberty, neurological function, and neurocognitive function of patients on

treatment, and to characterize the acceptability and palatability of F06 capsules and coated granule formulations.

Exploratory objectives were to identify molecular mechanism of resistance, to assess neurocognitive outcome in children, to assess bone biomarkers and bone growth.

- **Outcomes/endpoints**

- Overall Response Rate (ORR) by the BICR according to RECIST 1.1 or RANO criteria (based on confirmed responses in patients with measurable disease)

- Duration of Response (DOR)

- **Sample size**

3+3 design in the dose escalation part.

For Cohort B and D: The efficacy endpoint for each cohort was considered met if ⩾40% ORR (6 of 15 responses; 95% CI: 19.8%-64.3%) was observed following additional expansion.

- **Randomisation and Blinding (masking)**

Open-label single arm trial.

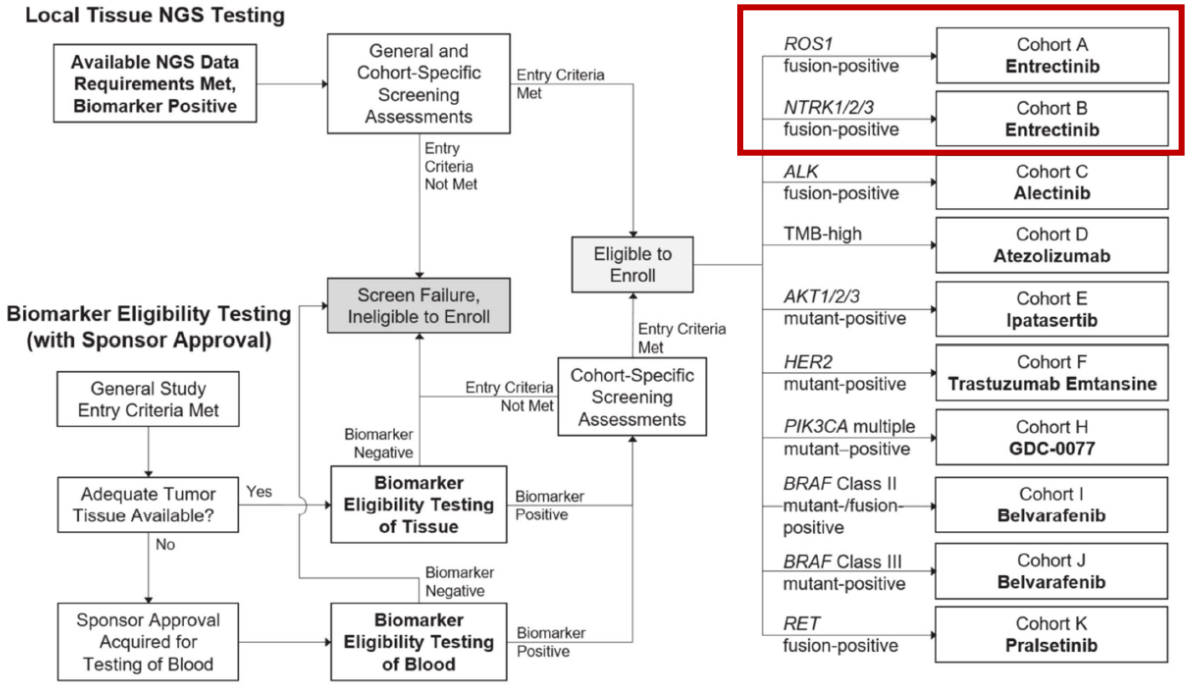
2.5.5.3. Supportive studies

TAPISTRY: Tumor-Agnostic Precision Immuno-oncology and Somatic Targeting Rational for You

TAPISTRY is a Phase II, global, multicenter, open-label, multi-cohort platform study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in adult and paediatric patients with unresectable, locally advanced or metastatic solid tumours determined to harbour specific oncogenic genomic alterations or who are tumour mutational burden (TMB)-high as identified by a validated NGS assay.

For the purpose of this submission, paediatric (age <18y) patients from Cohort A (patients with ROS1 fusion-positive solid tumours excluding NSCLC) and Cohort B (patients with NTRK1/2/3 fusion-positive tumours) were provided.

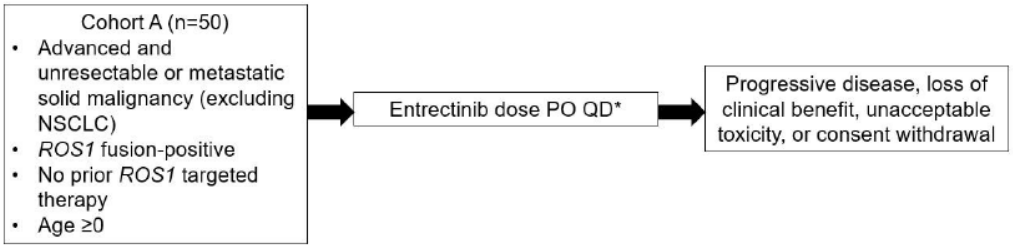
Figure 6: TAPISTRY overall study schema



NGS=next-generation sequencing; TMB=tumor mutational burden.

Note: If more than one alteration is identified, the priority for cohort assignment will be as described in the protocol, Section 3.1.1.

Figure 7: study schema: ROS1 Fusion-Positive Cohort

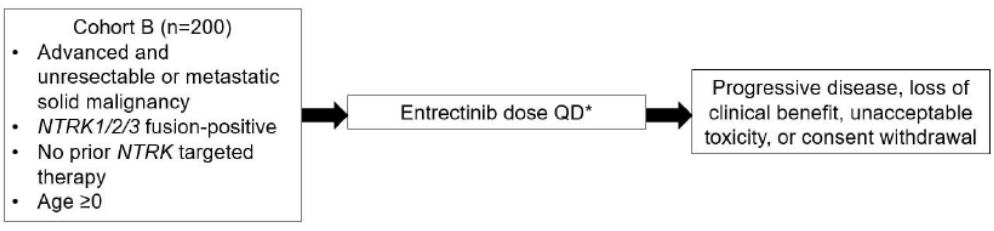


NSCLC=non–small cell lung cancer; PO=by mouth; QD=daily.

Note: Total planned enrollment for the *ROS1* fusion-positive cohort is approximately 50 patients. An interim futility analysis will be conducted on the first 25 efficacy-evaluable patients with solid tumors who are enrolled. Enrollment will not be paused while awaiting results of the futility analysis.

* See Section 2.1.7 for pediatric dosing guidelines.

Figure 8 : study schema: NTRK1/2/3 Fusion-Positive Cohort



QD=daily.

* See Section 2.1.7 for pediatric dosing guidelines.

In both Cohort A and B, patients received entrectinib once daily in repeated 28-day cycles. Dose recommendation was the same than in STARTRK-NG.

STARTRK-02

STARTRK-02 (GO40782) is an open-label, multicenter, global Phase II basket study of entrectinib for the treatment of patients with solid tumours that harbour an NTRK1/2/3, ROS1, or ALK gene rearrangement (fusion). This study enrolled eligible patients 18 years of age and above, though under the previous Sponsor (Ignyta), 2 paediatric (adolescent) patients who had no other treatment options available (the paediatric STARTRK-NG study was not yet active) were included in the study, both included in the ROS1 efficacy-evaluable population (see pooled analysis).

Entrectinib dose in those two paediatric patients was 600 mg per day (three 200-mg capsules).

Tumour assessments were performed at Screening, at the end of Cycle 1 and every 8 weeks. Radiographic confirmation of objective tumour response (no earlier than 4 weeks from the first response) or disease progression was based on RECIST v1.1. ORR as assessed by BICR was the primary endpoint of this study.

Additional supporting evidence provided:

Compassionate use: As of 28 February 2023, a total of 23 paediatric patients received entrectinib via the Compassionate Use Program, out of which 16 paediatric patients had data reported. For the 13 patients with NTRK fusion positive solid tumours (age range <1 – 11 years), 8 out of 9 of the patients with extracranial solid tumours were responders and all 4 patients with primary CNS tumours were responders. All 3 patients with ROS1 fusion positive tumours (primary CNS) were responders.

Natural history study (NTRK): "Characterization of Paediatric Cancer Patients with Solid Tumors with NTRK Fusions, Their Treatments and Outcomes on Non-Targeted Therapies"

The primary objective for this study is to characterize the natural history of paediatric patients with solid tumours harbouring an NTRK gene fusion and treated with historical standard of care (non-targeted) therapies. A comparison of the study data with historical patient level data from relevant databases and data sets was requested as part of the agreed PIP.

This study used secondary data from cohorts of patients with CNS and solid tumours with NTRK gene fusions aged <18 years from three sources: 1) Children's Hospital of Philadelphia (CHOP), A cohort of paediatric patients with solid tumours harbouring NTRK gene fusions created from the electronic health records (EHRs) of the CHOP; 2) CHU Sainte-Justine Research Centre in Montreal: the central nervous system NTRK fusion tumours (CNSonTRK) is a project driven by CHU Sainte-Justine that aims to get a comprehensive collection of TRK fusion-positive paediatric patients globally, retrieved in over 70 oncology centres worldwide; 3) Literature review of case reports of NTRK fusion-positive patients (Iannantuono et al 2022).

2.5.5.4. In vitro biomarker test for patient selection for efficacy

The procedures employed for patient selection and confirmation of eligible oncodriver fusions for inclusion of patients in the integrated efficacy analysis included:

- Confirmation of use of a Clinical Laboratory Improvement Amendments certified or equivalently accredited nucleic acid-based local test
- Adequate specimen nucleic acid sufficient for producing a reliable test result

- Presence of an NTRK-fusion/ROS1-fusion known to result in oncogenic driver activity
- Lack of co-occurrence with other strong oncodriver mutations likely to confer resistance

The molecular characterization of tumour tissue was evaluated by several different assay methods, but only patients harbouring gene fusions in NTRK/ROS1 that were detected by a nucleic acid-based diagnostic method and predicted to translate into a fusion protein with a functional kinase domain were considered to have a positive gene fusion status.

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analyses of efficacy supporting each paediatric indication (NTRK and ROS1 solid tumours) are presented below. Analyses were performed in patients enrolled in three studies (STARTRK-NG, TAPISTRY and STARTRK-2) up to 2 February 2022, with a clinical cut-off date of 2 August 2022 (i.e. at least 6 months of follow-up for all patients). During the procedure, updated analysis with CCOD 16 July 2023 and an enrolment cutoff date (ECOD) of 16 January 2023 to ensure at least 6 months of follow-up for the analysis were submitted (approximately 11 additional months of follow-up data and an additional 11 patients for NTRK evaluable for efficacy).

Methods

Tumour assessment

Tumour response was assessed using tumour imaging (CT or MRI scan). Screening tumour assessments were performed within 30 days prior to the first administration of entrectinib. On treatment tumour assessments were performed at end of every odd cycle (starting with Cycle 1) or whenever a clinical deterioration was observed and at End of Treatment (if not done in the previous 4 weeks). Tumour assessments could have been performed outside of the protocol-defined time points at the discretion of the investigator.

For patients with complete response (CR) or partial response (PR), response confirmation was performed no less than 4 weeks from when response criteria were first met. Tumour response was re-assessed at time of study drug discontinuation unless a tumour assessment had been performed within the previous 4 weeks.

An Independent Review Committee (IRC) conducted a BICR for response and progression of all patients, including a review of tumour assessment scans. All primary imaging data used for tumour assessment were collected by the Applicant to enable centralized, independent review. These reviews were performed prior to the primary and final efficacy analyses.

Endpoints

Primary Endpoint

Confirmed Objective Response Rate (ORR)

The primary endpoint for these studies is confirmed objective response rate (ORR), as assessed by BICR using RECIST v1.1 or RANO criteria.

Confirmed ORR was defined as the proportion of patients with confirmed complete response (CR) or partial response (PR); a confirmed response is a response that is sustained on repeat imaging ≥4 weeks after initial documentation of response. Such patients with a confirmed objective response (CR or PR) were referred to as

responders. Patients without a confirmed objective response, or without a post-baseline tumour assessment, were counted as non-responders.

Secondary Endpoints

Duration of Confirmed Response (DOR)

Duration of Confirmed Response was defined as the time from the first confirmed objective response (either CR or PR) to the first documentation of radiographic disease progression, as assessed by BICR using RECIST v1.1 or RANO criteria, or death due to any cause, whichever occurs first. Confirmed DOR was calculated only for responders (as defined above). Confirmed DOR was censored on the last tumour assessment date for patients without disease progression who have not died as of CCOD.

Time to Confirmed Response (TTR)

Confirmed TTR was defined as the time from the first dose of entrectinib to the first documentation of confirmed objective response (either CR or PR), as assessed by BICR using RECIST v1.1 or RANO criteria. Confirmed TTR data for patients without a confirmed objective response was censored on the date of the last tumour assessment (or, if no tumour assessment was performed after the baseline visit, at the date of first dose of entrectinib).

Clinical Benefit Rate (CBR)

The CBR was defined as the proportion of patients with CR, PR, or stable disease (SD) at 6 months after the first dose of entrectinib, as assessed by BICR using RECIST v1.1 or RANO criteria. Patients without a post-baseline tumour assessment were counted as not achieving clinical benefit.

Progression-Free Survival (PFS)

PFS was defined as the time from the first dose of entrectinib to the first documentation of radiographic disease progression by BICR assessment using RECIST v1.1 or RANO criteria or death due to any cause (whichever occurs first).

PFS data for patients without progression or death at the time of CCOD will be censored on the date of the last tumour assessment (or, if no tumour assessment was performed after the baseline visit, at the date of first dose of entrectinib).

Overall Survival (OS)

Overall survival (OS) was defined as the time from the first dose of entrectinib to the date of death due to any cause. Patients who are alive at the time of CCOD will be censored on the last known date that they were alive.

Efficacy Analysis

If not specified, the endpoints were assessed by BICR when applicable.

Table 23 : Summary of endpoints

Endpoints	Statistical Methods	Sensitivity/Subgroup Analysis

Confirmed Objective Response Rate	The number, proportion, and the corresponding 2-sided 95% Clopper-Pearson exact CI were summarized.	Sensitivity analysis: ORR assessed by Investigator ORR assessed by BICR and Investigator in patients with measurable baseline disease, respectively Subgroup analysis: ORR summarized by age ORR summarized by tumour type
Duration of Confirmed Response	The estimated median using the Kaplan-Meier method was presented. The associated 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982). The landmark analyses (e.g., at 6, 9, and 12 months) were also provided with the corresponding 2-sided 95% CIs calculated using Greenwood's formula. The summary statistics (mean, SD, median, IQR, minimum, maximum) of confirmed DOR were also provided.	Subgroup analysis: Confirmed DOR summarized by age Confirmed DOR summarized by tumour type
Time to Confirmed Response	The summary statistics (mean, SD, median, IQR, minimum, maximum) of confirmed TTR were provided. Additionally, the estimated median using the Kaplan-Meier method was presented. The associated 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982). The landmark analyses (e.g., at 6, 9, and 12 months) were also provided with the corresponding 2-sided 95% CIs calculated using Greenwood's formula.	Subgroup analysis: Confirmed TTR summarized by age Confirmed TTR summarized by tumour type
Clinical Benefit Rate	The number, proportion, and the corresponding 2-sided 95% Clopper-Pearson exact CI were summarized.	NA
Progression-Free Survival	The estimated median using the Kaplan-Meier method was presented. The associated 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982). The landmark analyses (e.g., at 6, 9, and 12 months) were also provided with the corresponding 2-sided 95% CIs calculated using Greenwood's formula.	Subgroup analysis: PFS summarized by age
Overall Survival	The estimated median using the Kaplan-Meier method was presented. The associated 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982). The landmark analyses (e.g., at 6, 9, and 12 months) were also provided with the corresponding 2-sided 95% CIs calculated using Greenwood's formula.	Subgroup analysis: OS summarized by age

CI = confidence interval; DOR = duration of confirmed response; IQR = interquartile range; NA = not applicable; ORR = confirmed objective response; OS = overall survival; PFS = progression-free survival; SD = standard deviation; TTR = time to confirmed response.

Results

NTRK POOLED ANALYSIS

The request for an extension of the previously approved indication in NTRK fusion positive solid tumours with no available treatment options in the paediatric population, from birth to ≤12 years of age (indication in age >12 and adults already granted) is based on updated efficacy data (CCOD 16 July 2023) from the NTRK Integrated Efficacy Population, which includes a total of 44 patients (range 1 month - 15 years); of those, 34 were from STARTRK-NG and 10 from TAPISTRY study. The NTRK Integrated Efficacy Population (n=44) includes patients who met all the following criteria:

- Age <18 years
- Had tumours that harbour an NTRK gene fusion (based on molecular characterization of tumour tissue as described above)
- No prior treatment with TRK inhibitors
- Measurable or evaluable disease at baseline
- Received at least 1 dose of entrectinib
- Had at least 6 months of follow-up

Compared with the dataset submitted initially (n=33), the updated analysis with CCOD of 16 July 2023 provided data from an additional 11 patients and up to approximately 11 months of additional follow-up.

Patient Disposition

A total of **44** patients were included in the NTRK integrated efficacy population (34 from STARTRK-NG, and 10 from TAPISTRY). At the CCOD (16 July 2023), the median duration of survival follow-up was 24.2 months (range: 1–66 months).

The median duration of treatment with entrectinib was 18.4 months (range: 0.8–56.0 months). Overall, 47.7% of patients (21/44) discontinued treatment at the CCOD, mostly due to progressive disease (7/21, 33.3%) followed by adverse event (5/21, 23.8%). Overall, 8 patients (18.2%) have discontinued the study, 7 for death and 1 lost to follow-up.

Baseline data

Table 24: Demographic and Baseline Characteristics, NTRK Integrated Analysis Population

Demographic and Baseline Characteristics, NTRK Safety-Evaluable Population, Patients (<18 years old), Patients Enrolled before or on the 16 Jan 2023
Protocols: CO40778, BO41932

	STARTRK-NG (N=34)	TAPISTRY (N=10)	Total (N=44)
Sex			
n	34	10	44
Male	15 (44.1%)	5 (50.0%)	20 (45.5%)
Female	19 (55.9%)	5 (50.0%)	24 (54.5%)
Age (years)			
n	34	10	44
mean	5.4	2.9	4.8
std	4.5	4.8	4.6
median	4.0	1.0	4.0
Q1, Q3	1, 9	0, 3	1, 7
Min, Max	0, 15	0, 15	0, 15
Age group			
>= 0 to < 28 days	0	0	0
>= 28 days to < 24 months	9 (26.5%)	5 (50.0%)	14 (31.8%)
>= 24 months to < 12 years	20 (58.8%)	4 (40.0%)	24 (54.5%)
>= 12 years to < 18 years	5 (14.7%)	1 (10.0%)	6 (13.6%)
Ethnicity			
n	34	10	44
Hispanic or Latino	4 (11.8%)	0	4 (9.1%)
Not Hispanic or Latino	21 (61.8%)	10 (100%)	31 (70.5%)
Not Stated	3 (8.8%)	0	3 (6.8%)
Unknown	6 (17.6%)	0	6 (13.6%)
Race			
n	34	10	44
Asian	9 (26.5%)	6 (60.0%)	15 (34.1%)
Black or African American	1 (2.9%)	0	1 (2.3%)
White	19 (55.9%)	4 (40.0%)	23 (52.3%)
Other	5 (14.7%)	0	5 (11.4%)
Weight (kg)			
n	34	10	44
mean	23.81	17.44	22.37
std	17.02	21.15	17.98
median	18.65	10.90	18.00
Q1, Q3	13.0, 33.7	7.5, 14.9	11.2, 27.6
Min, Max	3.5, 68.4	3.8, 75.5	3.5, 75.5
Height (cm)			
n	34	10	44
mean	109.02	88.68	104.40
std	32.73	38.18	34.66
median	107.50	79.50	103.30
Q1, Q3	85.0, 137.4	62.5, 97.4	83.0, 121.8
Min, Max	52.0, 176.9	51.0, 176.5	51.0, 176.9

	STARTRK-NG (N=34)	TAPISTRY (N=10)	Total (N=44)
BSA (m2)			
n	34	10	44
mean	0.83	0.63	0.78
std	0.41	0.49	0.44
median	0.74	0.50	0.73
Q1, Q3	0.6, 1.2	0.3, 0.6	0.5, 1.0
Min, Max	0.2, 1.8	0.2, 1.9	0.2, 1.9
BMI (kg/m^2)			
n	34	10	44
mean	17.55	17.56	17.55
std	3.37	2.96	3.25
median	16.29	17.65	17.03
Q1, Q3	15.2, 18.8	14.8, 18.4	15.2, 18.6
Min, Max	12.3, 26.6	13.9, 24.2	12.3, 26.6
Baseline Lansky/Karnofsky Score			
n	34	10	44
60	2 (5.9%)	0	2 (4.5%)
70	0	1 (10.0%)	1 (2.3%)
80	9 (26.5%)	1 (10.0%)	10 (22.7%)
90	9 (26.5%)	1 (10.0%)	10 (22.7%)
100	14 (41.2%)	7 (70.0%)	21 (47.7%)

The youngest patient at enrollment is 1.3 months.
Age is calculated as (Date of informed consent - Date of Birth + 1)/365.25. If the date of birth was partially collected, it was imputed to the 15th of June unless the patient was born in the same year as the year of the informed consent. In this last case, the 1st of Jan. was used.
STARTRK-NG = study CO40778, TAPISTRY = study BO41932
CCOD: Jul 16 2023, DBL: Sep 7 2023 (CO40778, BO41932)

Table 25: Baseline Disease Characteristics, NTRK Integrated Analysis Population

Disease Characteristics and History, NTRK Safety-Evaluable Population, Patients (<18 years old),
Patients Enrolled before or on the 16 Jan 2023
Protocols: CO40778, BO41932

	STARTRK-NG (N=34)	TAPISTRY (N=10)	Total (N=44)
Gene Fusion (NTRK1)			
n	14	3	17
ARHGEF2-NTRK1	1 (7.1%)	0	1 (5.9%)
BCAN-NTRK1	1 (7.1%)	0	1 (5.9%)
KIF21B-NTRK1	1 (7.1%)	0	1 (5.9%)
LMNA-NTRK1	5 (35.7%)	1 (33.3%)	6 (35.3%)
TPM3-NTRK1	3 (21.4%)	1 (33.3%)	4 (23.5%)
TPR-NTRK1	3 (21.4%)	1 (33.3%)	4 (23.5%)
Gene Fusion (NTRK2)			
n	9	1	10
AMOTL2-NTRK2	1 (11.1%)	0	1 (10.0%)
BCR-NTRK2	1 (11.1%)	0	1 (10.0%)
CASK-NTRK2	1 (11.1%)	0	1 (10.0%)
DNM3-NTRK2	1 (11.1%)	0	1 (10.0%)
EML1-NTRK2	1 (11.1%)	0	1 (10.0%)
GKAP1-NTRK2	1 (11.1%)	0	1 (10.0%)
KANK1-NTRK2	1 (11.1%)	0	1 (10.0%)
KIF5B-NTRK2	1 (11.1%)	0	1 (10.0%)
QKI-NTRK2	1 (11.1%)	0	1 (10.0%)
TNS3-NTRK2	0	1 (100%)	1 (10.0%)
Gene Fusion (NTRK3)			
n	11	6	17
EML4-NTRK3	1 (9.1%)	1 (16.7%)	2 (11.8%)
ETV6-NTRK3	7 (63.6%)	4 (66.7%)	11 (64.7%)
LMNA-NTRK3	0	1 (16.7%)	1 (5.9%)
MSN-NTRK3	1 (9.1%)	0	1 (5.9%)
PARP6-NTRK3	1 (9.1%)	0	1 (5.9%)
TFG-NTRK3	1 (9.1%)	0	1 (5.9%)
Primary Diagnosis			
n	34	10	44
CNS PRIMARY	18 (52.9%)	2 (20.0%)	20 (45.5%)
KIDNEY	0	1 (10.0%)	1 (2.3%)
SARCOMA	14 (41.2%)	7 (70.0%)	21 (47.7%)
SKIN CANCER	1 (2.9%)	0	1 (2.3%)
THYROID	1 (2.9%)	0	1 (2.3%)

Histology			
n	34	10	44
ANAPLASTIC ASTROCYTOMA	1 (2.9%)	0	1 (2.3%)
ANAPLASTIC GANGLIOGLIOMA	1 (2.9%)	0	1 (2.3%)
ASTROCYTOMA	0	1 (10.0%)	1 (2.3%)
DIFFUSE MIDLINE GLIOMA	1 (2.9%)	0	1 (2.3%)
FIBROSARCOMA	0	4 (40.0%)	4 (9.1%)
GANGLIONEUROBLASTOMA	1 (2.9%)	0	1 (2.3%)
GLIOBLASTOMA	4 (11.8%)	0	4 (9.1%)
GLIOMA	6 (17.6%)	1 (10.0%)	7 (15.9%)
GLIONEURONAL	3 (8.8%)	0	3 (6.8%)
INFANTILE FIBROSARCOMA	7 (20.6%)	0	7 (15.9%)
MEDULLOBLASTOMA	1 (2.9%)	0	1 (2.3%)
MELANOMA	1 (2.9%)	0	1 (2.3%)
OTHER	0	1 (10.0%)	1 (2.3%)
PAPILLARY THYROID	1 (2.9%)	0	1 (2.3%)
SARCOMA OTHER	1 (2.9%)	1 (10.0%)	2 (4.5%)
SPINDLE CELL	6 (17.6%)	2 (20.0%)	8 (18.2%)
Time Since Diagnosis (Months)			
n	34	10	44
mean	20.15	16.87	19.40
std	28.98	34.93	30.03
median	8.95	3.76	4.70
Q1, Q3	3.40, 19.30	1.61, 4.44	3.10, 19.25
Min, Max	0.9, 134.1	0.8, 111.9	0.8, 134.1
Extent of Disease			
n	32	10	42
LOCALLY ADVANCED	22 (68.8%)	10 (100%)	32 (76.2%)
METASTATIC DISEASE	10 (31.3%)	0	10 (23.8%)
Metastatic Sites			
n	10	0	10
Brain	3 (8.8%)	0	3 (6.8%)
Lung	3 (8.8%)	0	3 (6.8%)
Other	4 (11.8%)	0	4 (9.1%)

Patients may have multiple sites of metastases at baseline.
Two pediatric patients had disease that was neither locally advanced nor metastatic. Thus, their data of the extent of disease was not captured.
STARTRK-NG = study CO40778, TAPISTRY = study BO41932
CCOD: Jul 16 2023, DBL: Sep 7 2023 (CO40778, BO41932)

Program: root/clinical studies/RO7102122/share/pool EMA 2023/prod/program/t dm dh.sas
Output:
root/clinical studies/RO7102122/share/pool EMA 2023/prod/output/t dm dh NEEPED AGE18 ENRJAN23 PEDSCE
.out
19OCT2023 2:46
Page 2 of 2

Out of the total 44 patients, 36 of them had measurable disease at baseline per BICR.

Of the 39 patients in the NTRK population, 34 (87.2%) were enrolled based on a fusion-positive result from a site-directed local test, and 5 (12.8%) were enrolled based on a fusion positive result from Sponsor central testing. Of patients enrolled via local testing, only in 8 central retests were successful, with NTRK fusions confirmed by central test in 5 (62.5%).

Table 26 : Previous Cancer Treatments, NTRK Integrated Analysis Population

Previous Cancer Treatments, NTRK Safety-Evaluable Population, Patients (<18 years old), Patients Enrolled before or on the 16 Jan 2023
Protocols: CO40778, BO41932

	STARTRK-NG (N=34)	TAPISTRY (N=10)	Total (N=44)
Any previous therapy	23 (67.6%)	2 (20.0%)	25 (56.8%)
Any Chemotherapy	20 (58.8%)	2 (20.0%)	22 (50.0%)
Any Immunotherapy	1 (2.9%)	0	1 (2.3%)
Any targeted therapy	4 (11.8%)	0	4 (9.1%)
Any other therapy	2 (5.9%)	0	2 (4.5%)
Any previous radiotherapy	8 (23.5%)	0	8 (18.2%)
Any previous surgeries	19 (55.9%)	5 (50.0%)	24 (54.5%)
Prior lines of systemic therapy			
n	34	10	44
0	11 (32.4%)	8 (80.0%)	19 (43.2%)
1	12 (35.3%)	1 (10.0%)	13 (29.5%)
2	5 (14.7%)	0	5 (11.4%)
3	3 (8.8%)	1 (10.0%)	4 (9.1%)
4	1 (2.9%)	0	1 (2.3%)
>4	2 (5.9%)	0	2 (4.5%)

All prior surgeries, excluding the ones with intent of surgery as 'Diagnostic' are included.
STARTRK-NG = study CO40778, TAPISTRY = study BO41932
CCOD: Jul 16 2023, DBL: Sep 7 2023 (CO40778, BO41932)

Outcomes and estimation

Table 27 : Overview of Efficacy for Patients with NTRK Fusion-Positive Tumours

	August 2022 CCOD	March 2023 CCOD	July 2023 CCOD
	N=33	N=39	N=44
Confirmed Objective Response (BICR-assessed)			
ORR, n (%) [95% CI]	23 (69.7%) (51.3, 84.4)	28 (71.8%) (55.1, 85.0)	32 (72.7%) (57.2, 85.0)
Complete Response, n (%) Partial Response, n (%) Stable Disease, n (%)	14 (42.4%) 9 (27.3%) 6 (18.2%)	17 (43.6%) 11 (28.2%) 7 (17.9%)	20 (45.5%) 12 (27.3%) 8 (18.2%)
Non-CR/Non-PD, n (%)	2 (6.1%)	2 (5.1%)	2 (4.5%)
Progressive Disease, n (%)	2 (6.1%)	2 (5.1%)	2 (4.5%)
Not Evaluable, n (%)	0	0	0
Duration of Confirmed Objective Response (DOR) (BICR-assessed)			
Patients included in analysis n	23	28	32

Patients with event n (%) Patients without event n (%) Time to event, median (95% CI), months	5 (21.7%) 18 (78.3%) 25.4 (14.3, NE)	6 (21.4%) 22 (78.6%) NE (25.4, NE)	6 (18.8%) 26 (81.3%) NE (25.4, NE)
Time to Confirmed Objective Response (BICR-assessed)			
Patients included in analysis n	23	28	32
Mean (Std Dev), months Median (months) Range (min-max), months	1.89 (0.39) 1.84 1.1-3.5	2.07 (1.10) 1.84 1.1-7.4	2.05 (0.79) 1.86 1.1-5.5
Clinical Benefit Rate (BICR-assessed)			
Patients included in analysis, n	33	39	44
Clinical Benefit Rate, n (%) [95% CI]	28 (84.8%) 68.1, 94.9	34 (87.2%) 72.57, 95.70	38 (86.4%) 72.65, 94.83

Table 28: Confirmed Objective Response Rate (BICR Assessment), NTRK Integrated Analysis Population

Confirmed Objective Response Rate (BICR Assessment), NTRK Safety-Evaluable Population, Patients Enrolled before or on the 16 Jan 2023, Patients (<18 years old)
Protocols: CO40778, BO41932

	Total (N=44)
Responders	32 (72.7%)
95% CI	(57.21, 85.04)
Complete Response (CR)	20 (45.5%)
95% CI	(30.39, 61.15)
Partial Response (PR)	12 (27.3%)
95% CI	(14.96, 42.79)
Stable Disease (SD)	8 (18.2%)
95% CI	(8.19, 32.71)
Non-CR/Non-PD	2 (4.5%)
95% CI	(0.56, 15.47)
Progressive Disease (PD)	2 (4.5%)
95% CI	(0.56, 15.47)
Not Evaluable (NE)	0
Missing	0

Confidence Interval is calculated using Clopper-Pearson exact confidence interval.

CCOD: Jul 16 2023, DBL: Sep 7 2023 (CO40778, BO41932)

Higher confirmed ORR was seen by investigator assessment (ORR 79.5% (35/44), 95% CI: 64.7, 90.2), and in patients with measurable disease (36/44) by BICR at baseline (30/36 patients) (ORR 83.3%, 95% CI: 67.2, 93.6).

Figure 9 : Waterfall Plot: Best Percent Change from Baseline in Tumour Size (BICR Assessment), NTRK Integrated Analysis Population

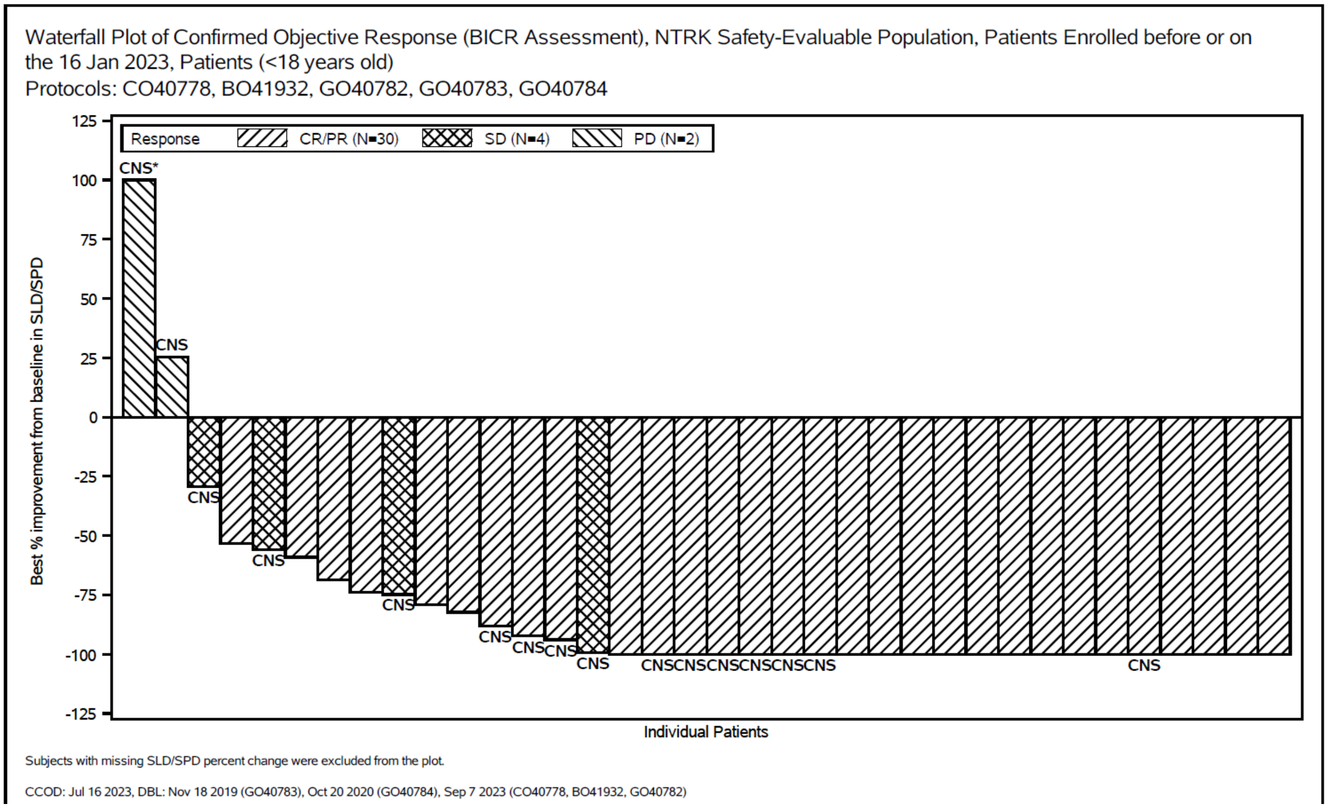
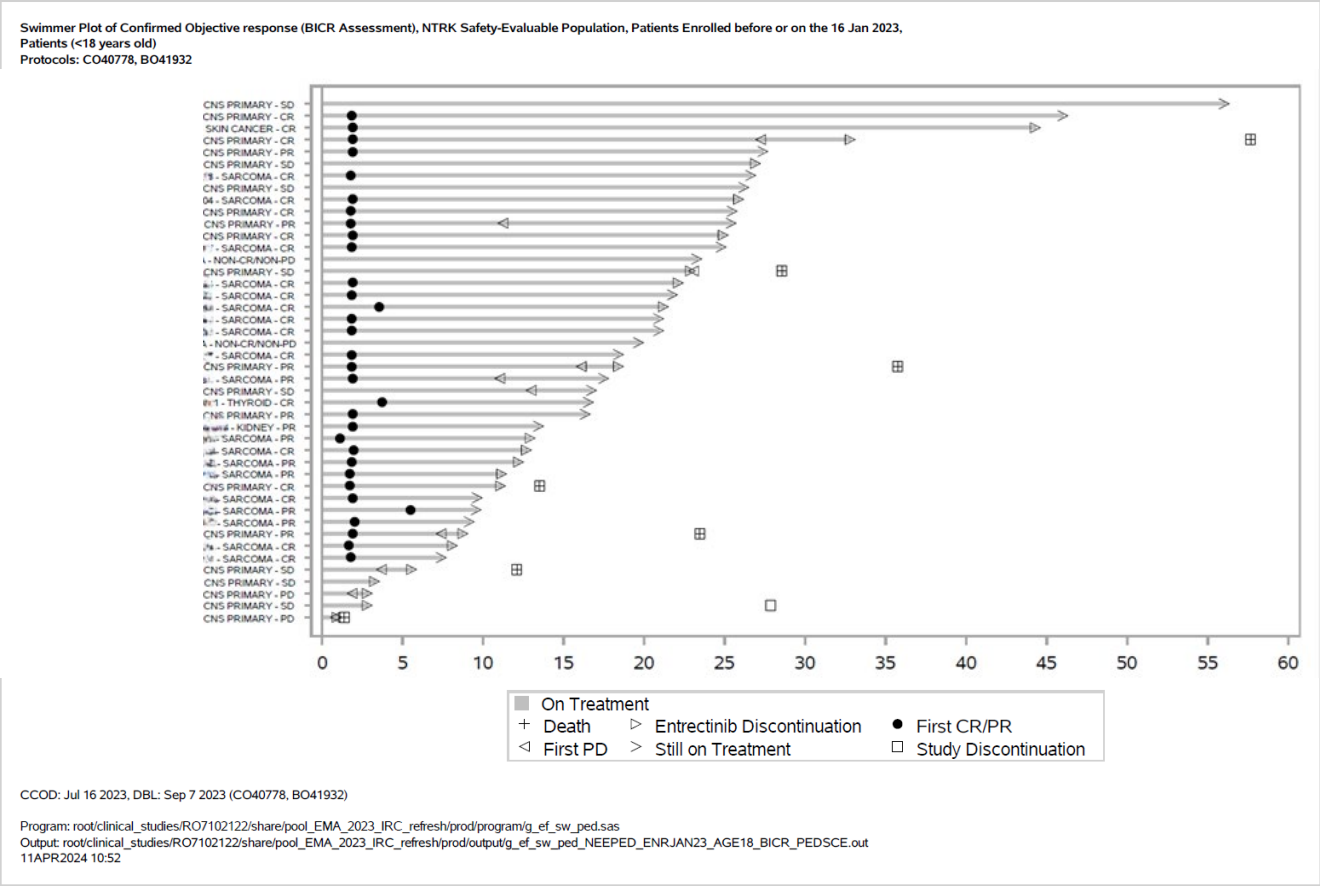


Figure 10: Swimmer Plot of Confirmed Objective Response (BICR Assessment), NTRK Integrated Analysis Population



ORR by Age:

Table 29: Confirmed Objective Response Rate (BICR Assessment) by Age, NTRK Integrated Analysis Population

	>= 28 days to < 24 months (N=14)	>= 24 months to < 12 years (N=24)	>= 12 years to < 18 years (N=6)	Total (N=44)
Responders	9 (64.3%)	19 (79.2%)	4 (66.7%)	32 (72.7%)
95% CI	(35.14, 87.24)	(57.85, 92.87)	(22.28, 95.67)	(57.21, 85.04)
Complete Response (CR)	7 (50.0%)	11 (45.8%)	2 (33.3%)	20 (45.5%)
95% CI	(23.04, 76.96)	(25.55, 67.18)	(4.33, 77.72)	(30.39, 61.15)
Partial Response (PR)	2 (14.3%)	8 (33.3%)	2 (33.3%)	12 (27.3%)
95% CI	(1.78, 42.81)	(15.63, 55.32)	(4.33, 77.72)	(14.96, 42.79)
Stable Disease (SD)	4 (28.6%)	3 (12.5%)	1 (16.7%)	8 (18.2%)
95% CI	(8.39, 58.10)	(2.66, 32.36)	(0.42, 64.12)	(8.19, 32.71)
Non-CR/Non-PD	1 (7.1%)	1 (4.2%)	0	2 (4.5%)
95% CI	(0.18, 33.87)	(0.11, 21.12)	(0.00, 45.93)	(0.56, 15.47)
Progressive Disease (PD)	0	1 (4.2%)	1 (16.7%)	2 (4.5%)
95% CI	(0.00, 23.16)	(0.11, 21.12)	(0.42, 64.12)	(0.56, 15.47)
Not Evaluable (NE)	0	0	0	0
Missing	0	0	0	0

Confidence Interval is calculated using Clopper-Pearson exact confidence interval.

CCOD: Jul 16 2023, DBL: Sep 7 2023 (CO40778, BO41932)

Table 30: Confirmed Objective Response Rate (BICR Assessment) by Age (0 to ≤6 years), NTRK Integrated Analysis Population (Jul 16 2023)

Age category:	0 to ≤6 years N=31	≥6 months to ≤2 years N=6	≥6 months to ≤6 years N=21
BICR-ORR, n (%)	22 (71.0%)	2 (33.3%)	14 (66.7%)
(95% CI)	(51.96, 85.78)	(4.33, 77.72)	(43.03, 85.41)
CR, n (%)	14 (45.2%)	1 (16.7%)	8 (38.1%)
PR, n (%)	8 (25.8%)	1 (16.7%)	6 (28.6%)
SD, n (%)	6 (19.4%)	2 (33.3%)	4 (19.0%)
non-CR/non-PD, n (%)	2 (6.5%)	2 (33.3%)	2 (9.5%)
PD, n (%)	1 (3.2%)	0	1 (4.8%)

BICR=blinded independent central review; CI=confidence interval; CR=complete response; ORR=objective response rate; PD=progressive disease; PR=partial response; SD=stable disease.

Clinical cutoff date: Jul 16 2023.

Patients with less than 6 months are 10, and 8 are responders (CCOD Jul 16 2023).

ORR and DOR by tumour type:

Table 31: Efficacy by Tumour Type in Paediatric Patients with NTRK Fusion-Positive Solid Tumours

Tumour type	Patients (n=44)	ORR		DOR
		n (%)	95% CI	Range (months)
Primary CNS	20	10 (50)	(27.2, 72.8)	5.5, 42.3*
Infantile fibrosarcoma	11	10 (90.9)	(58.7, 99.8)	5.7*, 24*
Spindle Cell	8	8 (100.0)	(63.1, 100)	5.4*, 23*
Sarcoma (other)	2	PR; Non-CR/Non-PD	NA	3.7*
Melanoma	1	CR	NA	42.4*
Kidney cancer	1	PR	NA	9.2*
Thyroid cancer	1	CR	NA	11.1*

*Censored

ORR: Objective Response Rate; DOR: Duration of Response; NA: not applicable due to small number or lack of response; CR: complete response; PR: partial response; PD: progressive disease

Three of the patients with primary CNS tumours had non-target/non-measurable disease only at baseline and could therefore only have SD as the best response per Response Assessment in Neuro-Oncology (RANO criteria).

ORR in non-primary CNS tumours overall was 91.7% (22/24).

Five of the patients with non-CNS tumours had non-target/non-measurable disease only at baseline. Two of these patients could only be classified as non-CR/non-PD per RECIST. Two patients achieved CR and 1 patient was missing the response assessment.

ORR by BSA category

Table 32 : Confirmed Objective Response Rate (BICR Assessment) by BSA Category, NTRK Integrated Analysis Population (CCOD 16 July 2023)

BSA category:	**--**	**I**	**IIa**	**IIb**
	BSA<0.43 m^2	**0.43-0.50 m^2**	**0.51-0.65 m^2**	**0.66-0.80 m^2**
	N=10	**N=1**	**N=9**	**N=11**
BICR-ORR, n (%)	8 (80.0%)	0	5 (55.6%)	9 (81.8%)
(95% CI)	(44.39, 97.48)	--	(21.20, 86.30)	(48.22, 97.72)
CR, n (%)	6 (60.0%)	0	2 (22.2%)	5 (45.5%)
PR, n (%)	2 (20.0%)	0	3 (33.3%)	4 (36.4%)
SD, n (%)	2 (20.0%)	0	3 (33.3%)	1 (9.1%)
non-CR/non-PD, n (%)	0	1 (100%)	1 (11.4%)	0
PD, n (%)	0	0	0	1 (9.1%)

BICR=blinded independent central review; BSA=body surface area; CI=confidence interval; CR=complete response; ORR=objective response rate; PD=progressive disease; PR = partial response; SD=stable disease.

Clinical cutoff date: July 2023.

ORR was similar regardless the local or central molecular testing site.

ROS1 POOLED ANALYSIS

To support an extension of indication in paediatric patients (from birth to <18 years) with ROS1 fusion positive solid tumours with no satisfactory treatment options, the MAH submitted updated efficacy data from the **ROS1 Integrated Efficacy Population**, which includes a total of **19 patients** (range 3 months - 15 years); of those, 16 were from STARTRK-NG, 2 from STARTRK-02 and 1 from TAPISTRY study. The ROS1 Integrated Efficacy Population (n=19) includes patients who met all the following criteria:

- Age <18 years
- Had tumours that harbour a ROS1 gene fusion (based on molecular characterization of tumour tissue as described in Section 2.6 above)
- No prior treatment with ROS1 inhibitors
- Measurable or evaluable disease at baseline
- Received at least 1 dose of entrectinib
- Had at least 6 months of follow-up

As compared to the initially submitted data cut, updated analysis with CCOD of 8 March 2023 provided data from an additional 3 patients and up to approximately 7 months of additional follow-up.

Patient Disposition

A total of 19 patients were included in the ROS1 integrated efficacy population. As of the updated CCOD (8 March 2023), the median duration of treatment with entrectinib was 12.2 months (range: 1.2-35.7 months). The median duration of survival follow-up was 28 months (range: 1-69 months). At the time of the CCOD, most of the patients were still on study (n=15, 78.9%), although most of them have discontinued treatment (n=12, 63.2%). Drug discontinuation occurred mostly for adverse event (5/12, 41.7%).

Baseline data

Table 33: Demographic and Baseline Characteristics, ROS1 Integrated Analysis Population

Demographic and Baseline Characteristics, ROS1 Safety-Evaluable Population, Patients (<18 years old)
Protocols: CO40778, BO41932, GO40782

	STARTRK-NG (N=16)	TAPISTRY (N=1)	STARTRK-02 (N=2)	Total (N=19)
Sex				
n	16	1	2	19
Male	8 (50.0%)	0	1 (50.0%)	9 (47.4%)
Female	8 (50.0%)	1 (100%)	1 (50.0%)	10 (52.6%)
Age (years)				
n	16	1	2	19
mean	6.3	10.0	15.0	7.4
std	4.3	NE	0.0	4.8
median	7.0	10.0	15.0	8.0
Q1, Q3	3, 10	10, 10	15, 15	3, 11
Min, Max	0, 14	10, 10	15, 15	0, 15
Age group				
>= 0 to < 28 days	0	0	0	0
>= 28 days to < 24 months	3 (18.8%)	0	0	3 (15.8%)
>= 24 months to < 12 years	12 (75.0%)	1 (100%)	0	13 (68.4%)
>= 12 years to < 18 years	1 (6.3%)	0	2 (100%)	3 (15.8%)
Ethnicity				
n	16	1	2	19
Hispanic or Latino	2 (12.5%)	0	1 (50.0%)	3 (15.8%)
Not Hispanic or Latino	14 (87.5%)	1 (100%)	1 (50.0%)	16 (84.2%)
Race				
n	16	1	2	19
Asian	3 (18.8%)	0	0	3 (15.8%)
Black or African American	1 (6.3%)	0	0	1 (5.3%)
White	12 (75.0%)	1 (100%)	2 (100%)	15 (78.9%)
Weight (kg)				
n	16	1	2	19
mean	23.14	36.00	50.85	26.73
std	10.43	NE	4.45	13.14
median	22.95	36.00	50.85	28.00
Q1, Q3	16.8, 31.1	36.0, 36.0	47.7, 54.0	18.6, 34.9
Min, Max	6.0, 41.0	36.0, 36.0	47.7, 54.0	6.0, 54.0
Height (cm)				
n	16	1	2	19
mean	117.31	133.00	167.20	123.39
std	31.68	NE	3.11	32.98
median	125.80	133.00	167.20	130.00
Q1, Q3	98.0, 136.5	133.0, 133.0	165.0, 169.4	100.0, 154.5
Min, Max	61.0, 158.0	133.0, 133.0	165.0, 169.4	61.0, 169.4
BSA (m2)				
n	16	1	2	19
mean	0.86	1.15	1.55	0.95
std	0.31	NE	0.04	0.36
median	0.91	1.15	1.55	1.01
Q1, Q3	0.7, 1.1	1.2, 1.2	1.5, 1.6	0.8, 1.2
Min, Max	0.3, 1.3	1.2, 1.2	1.5, 1.6	0.3, 1.6
BMI (kg/m^2)				
n	16	1	2	19
mean	16.13	20.35	18.23	16.57
std	2.52	NE	2.27	2.62
median	16.35	20.35	18.23	16.43
Q1, Q3	14.3, 18.3	20.4, 20.4	16.6, 19.8	14.4, 18.5
Min, Max	11.3, 20.1	20.4, 20.4	16.6, 19.8	11.3, 20.4
Baseline Lansky/Karnofsky Score				
n	16	1	0	17
70	1 (6.3%)	0	0	1 (5.9%)
80	2 (12.5%)	1 (100%)	0	3 (17.6%)
90	5 (31.3%)	0	0	5 (29.4%)
100	8 (50.0%)	0	0	8 (47.1%)

The youngest patient at enrollment is 3.0 months.
Age is calculated as (Date of informed consent - Date of Birth + 1)/365.25. If the date of birth was partially collected, it was imputed to the 15th of June unless the patient was born in the same year as the year of the informed consent. In this last case, the 1st of Jan. was used.
STARTRK-NG = study CO40778, TAPISTRY = study BO41932, STARTRK-02 = study GO40782.
CCOD: Mar 08 2023, DBL: Apr 28 2023 (CO40778 and GO40782), May 2 2023 (BO41932)
Patients Enrolled up to September 08, 2022.

Table 34: Baseline Disease Characteristics, ROS1 Integrated Analysis Population

Baseline Disease Characteristics, ROS1 Safety-Evaluable Population, Patients (<18 years old)
Protocols: CO40778, BO41932, GO40782

	STARTRK-NG (N=16)	TAPISTRY (N=1)	STARTRK-02 (N=2)	Total (N=19)
Gene Fusion				
n	16	1	2	19
EEF1G-ROS1	1 (6.3%)	0	0	1 (5.3%)
EZR-ROS1	0	0	1 (50.0%)	1 (5.3%)
FN1-ROS1	1 (6.3%)	0	0	1 (5.3%)
GOPC-ROS1	4 (25.0%)	0	1 (50.0%)	5 (26.3%)
SLC35F1-ROS1	0	1 (100%)	0	1 (5.3%)
TFG-ROS1	10 (62.5%)	0	0	10 (52.6%)
Primary Diagnosis				
n	16	1	2	19
CNS PRIMARY	6 (37.5%)	1 (100%)	1 (50.0%)	8 (42.1%)
NSCLC	0	0	1 (50.0%)	1 (5.3%)
SARCOMA	10 (62.5%)	0	0	10 (52.6%)
Histology				
n	16	1	2	19
ANAPLASTIC ASTROCYTOMA	1 (6.3%)	0	0	1 (5.3%)
ASTROCYTOMA	1 (6.3%)	0	0	1 (5.3%)
GLIOBLASTOMA	0	1 (100%)	0	1 (5.3%)
GLIOMA	2 (12.5%)	0	0	2 (10.5%)
GLIONEURONAL	0	0	1 (50.0%)	1 (5.3%)
INFANTILE FIBROSARCOMA	2 (12.5%)	0	0	2 (10.5%)
INFLAMMATORY MYOFIBROBLASTIC TUMOR	8 (50.0%)	0	0	8 (42.1%)
NSCLC - NOS	0	0	1 (50.0%)	1 (5.3%)
PILOCYTIC ASTROCYTOMA	1 (6.3%)	0	0	1 (5.3%)
SPINDLE CELL	1 (6.3%)	0	0	1 (5.3%)
Time Since Diagnosis (Months)				
n	16	1	2	19
mean	10.46	23.98	40.30	14.31
std	17.49	NE	56.14	22.88
median	2.91	23.98	40.30	3.15
Q1, Q3	1.4, 13.8	24.0, 24.0	0.6, 80.0	1.3, 18.9
Min, Max	0.3, 68.4	24.0, 24.0	0.6, 80.0	0.3, 80.0
Stage at Initial Diagnosis				
n	16	1	2	19
0	0	1 (100%)	0	1 (5.3%)
I	1 (6.3%)	0	0	1 (5.3%)
IA	1 (6.3%)	0	0	1 (5.3%)
IB	2 (12.5%)	0	0	2 (10.5%)
II	1 (6.3%)	0	0	1 (5.3%)
III	1 (6.3%)	0	0	1 (5.3%)
IIIA	0	0	1 (50.0%)	1 (5.3%)
IV	1 (6.3%)	0	1 (50.0%)	2 (10.5%)
NA	9 (56.3%)	0	0	9 (47.4%)
Extent of Disease				
n	16	1	2	19
LOCALLY ADVANCED	15 (93.8%)	0	1 (50.0%)	16 (84.2%)
METASTATIC DISEASE	1 (6.3%)	1 (100%)	1 (50.0%)	3 (15.8%)
Metastatic Sites				
n	1	1	1	3
Brain	0	1 (100%)	0	1 (5.3%)
Lymph Nodes	0	0	1 (50.0%)	1 (5.3%)
Other	1 (6.3%)	0	1 (50.0%)	2 (10.5%)

Staging systems vary across disease histologies and there are some tumor types for which no formal staging system exists, some of which were captured as Stage 0 or NA.
STARTRK-NG = study CO40778, TAPISTRY = study BO41932, STARTRK-02 = study GO40782.
CCOD: Mar 08 2023, DBL: Apr 28 2023 (CO40778 and GO40782), May 2 2023 (BO41932)
Patients Enrolled up to September 08, 2022.

Of the 19 patients in the ROS1 population, 16 (84.2%) were enrolled based on a fusion-positive result from a site-directed local test, and 3 (15.8%) were enrolled based on a fusion-positive result from Sponsor central testing. Of patients enrolled via local testing, in 9 central retests were successful, with ROS1 fusions confirmed by central test in 8 of them (89%).

Table 35: Previous Cancer Treatments, ROS1 Integrated Analysis Population

Previous Cancer Treatments, ROS1 Safety-Evaluable Population, Patients (<18 years old)
Protocols: CO40778, BO41932, GO40782

	STARTRK-NG (N=16)	TAPISTRY (N=1)	STARTRK-02 (N=2)	Total (N=19)
Any previous therapy	7 (43.8%)	1 (100%)	0	8 (42.1%)
Any Chemotherapy	5 (31.3%)	1 (100%)	0	6 (31.6%)
Any Immunotherapy	1 (6.3%)	0	0	1 (5.3%)
Any targeted therapy	2 (12.5%)	1 (100%)	0	3 (15.8%)
Any other therapy	2 (12.5%)	0	0	2 (10.5%)
Any previous radiotherapy	1 (6.3%)	1 (100%)	1 (50.0%)	3 (15.8%)
Any previous surgeries	7 (43.8%)	1 (100%)	1 (50.0%)	9 (47.4%)
Prior lines of systemic therapy				
n	16	1	2	19
0	9 (56.3%)	0	2 (100%)	11 (57.9%)
1	4 (25.0%)	0	0	4 (21.1%)
2	0	1 (100%)	0	1 (5.3%)
3	1 (6.3%)	0	0	1 (5.3%)
4	1 (6.3%)	0	0	1 (5.3%)
>4	1 (6.3%)	0	0	1 (5.3%)

All prior surgeries, excluding the ones with intent of surgery as 'Diagnostic' are included.
STARTRK-NG = study CO40778, TAPISTRY = study BO41932, STARTRK-02 = study GO40782.
CCOD: Mar 08 2023, DBL: Apr 28 2023 (CO40778 and GO40782), May 2 2023 (BO41932)
Patients Enrolled up to September 08, 2022.

Outcomes and estimation

Table 36: Overview of Efficacy ROS1 Fusion-Positive Patients

	ROS1 N=16 (2 Aug 2022)	ROS1 N=19 (8 March 2023)
Confirmed Objective Response (BICR-assessed)		
ORR, n, (%) (95% CI)	10 (62.5%) (35.4, 84.8)	12 (63.2%) (38.36, 83.71)
Complete Response, n (%)	3 (18.8%)	3 (15.8%)
Partial Response, n (%)	7 (43.8%)	9 (47.4%)
Stable Disease, n (%)	5 (31.3%)	6 (31.6%)
Non-CR/Non-PD, n (%)	0	0
Progressive Disease, n (%)	0	0
Not Evaluable, n (%)	1 (6.3%)	1 (5.3%)
Duration of Confirmed Objective Response (DOR) (BICR-assessed)		
Patients included in analysis n	10	12
Patients with event n (%)	1 (10%)	1 (8.3%)
Patients without event n (%)	9 (90.0%)	11 (91.7%)
Time to event, median (95% CI), months	NE (16.2, NE)	NE (16.2, NE)
Time to Confirmed Objective Response (BICR-assessed)		
Patients included in analysis n	16	19
Mean (Std Dev), months	2.58 (1.03)	2.61 (1.01)
Median (months)	1.89	1.89
Range (Min-Max), months	1.6–4.0	1.6–4.0
Clinical Benefit Rate (BICR-assessed)		
Patients included in analysis n	16	19
Clinical Benefit Rate n (%)	13 (81.3%)	15 (78.9%)
95% CI	54.4, 96.0	54.43, 93.95
Progression-Free Survival (BICR-assessed)		
Patients included in analysis n	16	19
Patients with event n (%)	3 (18.8%)	5 (26.3%)
Patients without event n (%)	13 (81.3%)	14 (73.7%)
Median (95% CI), months	NE (18.1, NE)	NE (18.1, NE)
Overall Survival		
Patients included in analysis n	16	19
Patients with event n (%)	2 (12.5%)	3 (15.8%)
Patients without event n (%)	14 (87.5%)	16 (84.2%)
Median (95% CI), months	NE	NE

BICR=blinded independent central review; CR=complete response; NE=not estimable; PR=partial response.
Note: Includes patients with measurable or evaluable disease.

Table 37: Confirmed Objective Response Rate (BICR Assessment), ROS1 Integrated Analysis Population

Confirmed Objective Response Rate (BICR Assessment), ROS1 Safety-Evaluable Population, Patients (<18 years old)
Protocols: CO40778, BO41932, GO40782

	Total (N=19)
Responders	12 (63.2%)
95% CI	(38.36, 83.71)
Complete Response (CR)	3 (15.8%)
95% CI	(3.38, 39.58)
Partial Response (PR)	9 (47.4%)
95% CI	(24.45, 71.14)
Stable Disease (SD)	6 (31.6%)
95% CI	(12.58, 56.55)
Non-CR/Non-PD	0
95% CI	(0.00, 17.65)
Progressive Disease (PD)	0
95% CI	(0.00, 17.65)
Not Evaluable (NE)	1 (5.3%)
Missing	0

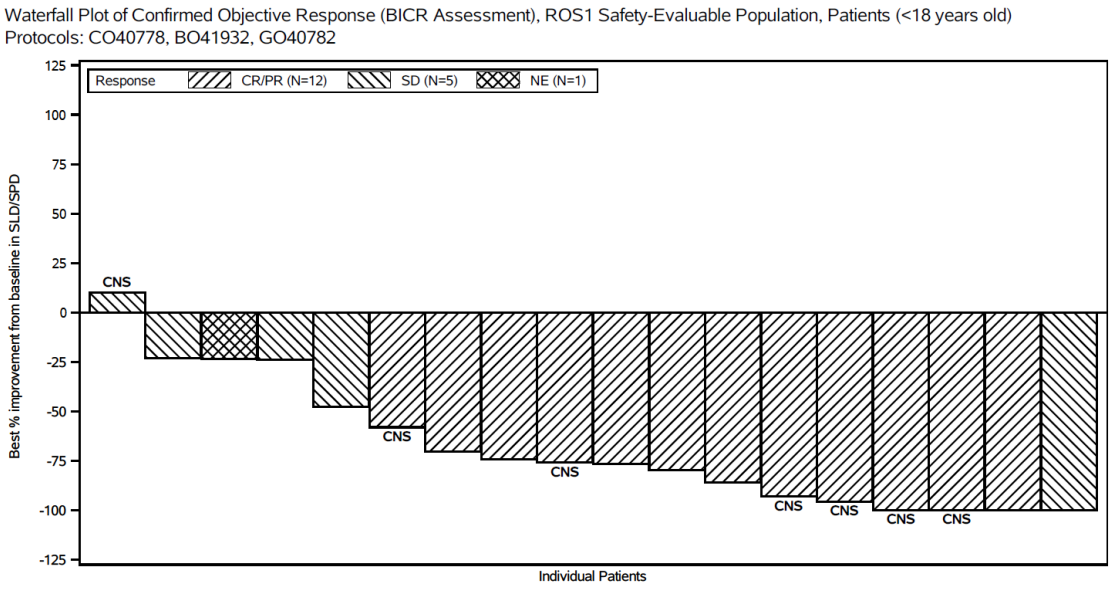
Confidence Interval is calculated using Clopper-Pearson exact confidence interval.

CCOD: Mar 08 2023, DBL: Apr 28 2023 (CO40778 and GO40782), May 2 2023 (BO41932)
Patients Enrolled up to September 08, 2022.

Confirmed ORR by the Investigator was achieved in 12/19 patients (63.2%; 95% CI: 38.4, 83.7) in the ROS1 integrated efficacy population.

Eighteen of the 19 patients (94.7%) in the ROS1 integrated efficacy population had measurable disease at baseline, and Confirmed Objective Response Rate by BICR in patients with Measurable Disease was 66.7% (95% CI: 40.99, 86.66) (12/18 responders).

Figure 11 : Waterfall Plot: Best Percent Change from Baseline in Tumour Size (BICR Assessment), ROS1 Integrated Analysis Population

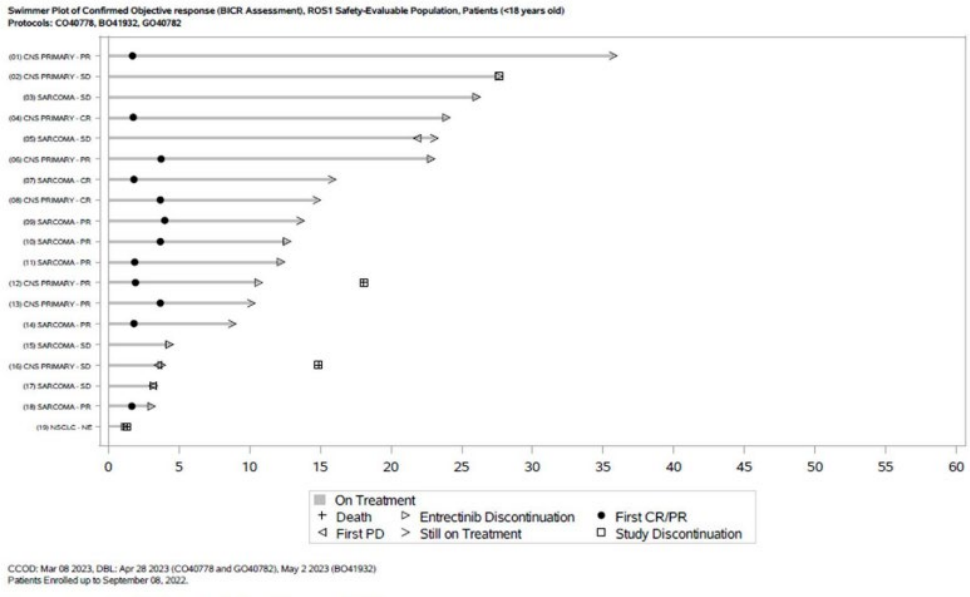


Abbreviations: SLD=Sum of Longest Diameters, SPD=Sum of Products of Greatest Diameters
Only patients with available baseline and post-baseline values for SLD or SPD were included in the plot.
*: Best percentage from baseline > 100%.

CCOD: Mar 08 2023, DBL: Apr 28 2023 (CO40778 and GO40782), May 2 2023 (BO41932)
Patients Enrolled up to September 08, 2022.

BICR = blinded Independent Central Review; CCOD = clinical cutoff date; CR = complete response; DBL = database lock; PD = progressive disease; PR = partial response; SD = stable disease.

Figure 12: Swimmer Plot of Confirmed Objective Response (BICR Assessment), ROS1 Integrated Analysis Population



Note: The x-axis is shown in months.

ORR by Age:

Table 38 : Confirmed Objective Response Rate (BICR Assessment) by Age, ROS1 Integrated Analysis Population

Confirmed Objective Response Rate (BICR Assessment) by Age Group, ROS1 Safety-Evaluable Population, Patients (<18 years old)
Protocols: CO40778, BO41932, GO40782

	>= 28 days to < 24 months (N=3)	>= 24 months to < 12 years (N=13)	>= 12 years to < 18 years (N=3)	Total (N=19)
Responders	1 (33.3%)	10 (76.9%)	1 (33.3%)	12 (63.2%)
95% CI	(0.84, 90.57)	(46.19, 94.96)	(0.84, 90.57)	(38.36, 83.71)
Complete Response (CR)	0	3 (23.1%)	0	3 (15.8%)
95% CI	(0.00, 70.76)	(5.04, 53.81)	(0.00, 70.76)	(3.38, 39.58)
Partial Response (PR)	1 (33.3%)	7 (53.8%)	1 (33.3%)	9 (47.4%)
95% CI	(0.84, 90.57)	(25.13, 80.78)	(0.84, 90.57)	(24.45, 71.14)
Stable Disease (SD)	2 (66.7%)	3 (23.1%)	1 (33.3%)	6 (31.6%)
95% CI	(9.43, 99.16)	(5.04, 53.81)	(0.84, 90.57)	(12.58, 56.55)
Non-CR/Non-PD	0	0	0	0
95% CI	(0.00, 70.76)	(0.00, 24.71)	(0.00, 70.76)	(0.00, 17.65)
Progressive Disease (PD)	0	0	0	0
95% CI	(0.00, 70.76)	(0.00, 24.71)	(0.00, 70.76)	(0.00, 17.65)
Not Evaluable (NE)	0	0	1 (33.3%)	1 (5.3%)
Missing	0	0	0	0

Confidence Interval is calculated using Clopper-Pearson exact confidence interval.

CCOD: Mar 08 2023, DBL: Apr 28 2023 (CO40778 and GO40782), May 2 2023 (BO41932)
Patients Enrolled up to September 08, 2022.

ORR by tumour type:

Table 39: Efficacy by Tumour Type in Paediatric Patients with ROS1 Fusion-Positive Solid Tumours

Tumor Type	Patients (N=19)	Confirmed ORR		Confirmed DOR
		n (%)	95% CI	Range (months)
All				
Primary CNS	8	6 (75.0%)	34.91, 96.81	5.6* - 31.3*
Inflammatory myofibroblastic tumor	7	3 (42.9%)	9.90, 81.59	5.7* - 10.4*
Infantile fibrosarcoma	2	2 (100.0%)	15.81, 100.00	8.8* - 12.9*
Spindle cell	1	PR	NA	1.7*
NSCLC- NOS	1	NE	NA	NA

DOR=Duration of Response; NA=not applicable due to small number or lack of response; NE=not evaluable; NOS=not otherwise specified; NSCLC=non-small cell lung cancer; ORR=Objective Response Rate; PR=partial response.
*Censored observation.

Note: one patient with IMT had intracranial IMT thus counted in the efficacy analysis as CNS primary.

ORR was similar regardless the local or central molecular testing site.

Table 40 : Duration of Confirmed Objective Response (BICR Assessment), ROS1 Integrated Analysis Population

Summary statistics of Duration of Confirmed Objective Response (BICR assessment), ROS1 Safety-Evaluable Population, Patients (<18 years old)
Protocols: CO40778, BO41932, GO40782

	Total (N=19)
Confirmed Objective Response Duration (months)	
n	12
mean	12.87
std	8.24
median	10.73
Q1, Q3	7.21, 17.66
Min, Max	1.7, 31.3
Duration of Response >= 6 months	9 (75.0%)
Duration of Response >= 9 months	8 (66.7%)
Duration of Response >= 12 months	5 (41.7%)
Duration of Response >= 18 months	3 (25.0%)
Duration of Response >= 24 months	1 (8.3%)

The target lesion for one patient was resected while the patient was on treatment, and the subsequent scan was recorded as PR post surgery not as NE per RANO criteria for BICR.
BICR was not provided with clinical surgical information.

CCOD: Mar 08 2023, DBL: Apr 28 2023 (CO40778 and GO40782), May 2 2023 (BO41932)
Patients Enrolled up to September 08, 2022.

Summary of main efficacy results

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 41: Summary of integrated efficacy results

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Patient updated efficacy data from STARTRK-NG, TAPISTRY, and STARTRK-02 studies have been pooled and analysed collectively as the NTRK/ROS1 integrated efficacy population (n=44/n=19) with a clinical cutoff date (CCOD) of 16 July 2023 for the NTRK integrated efficacy population and CCOD of 8 March 2023 for ROS1 integrated efficacy population and applying an enrolment cutoff date (ECOD) to ensure at least 6 months of follow-up for the analysis. The integrated efficacy population for the NTRK / ROS1 gene fusion group is composed of the 'NTRK / ROS1 safety-evaluable populations' from the individual studies, which included patients < 18 years old with NTRK / ROS1 fusion-positive tumours with no prior TRK / ROS1 inhibitor treatment who received any amount of entrectinib and had been followed up for at least 6 months from enrolment (NTRK ECOD: 16 January 2023; ROS1 ECOD: 8 September 2022) at the time of the clinical cutoff (NTRK: 16 July 2023; ROS1: 8 March 2023).		
Descriptive statistics and estimate variability	Treatment group	***NTRK* fusion-positive patients**	***ROS1* fusion-positive patients**
	Number of subjects	**44**	**19**
	BICR-assessed Confirmed ORR Number of responders n (%) (95% CI)	32 (72.7) (57.21, 85.04)	12 (63.2%) (38.36, 83.71)
	BICR-assessed Confirmed DOR Number of responders Median (95% CI) (months)	32 NE (25.4, NE)	12 NE (16.2, NE)
	BICR-assessed confirmed TTR Number of responders Median (Min-Max) (months)	30 1.9 (1.1–7.4)	19 1.89 (1.6-4.0)
	BICR-assessed PFS Patients included in analysis n Median (95% CI)	44 NE (23.1, NE)	19 NE (18.1, NE)
	Overall Survival Patients included in analysis n Median (95% CI)	44 NE (35.7, NE)	19 NE
Notes	Patients with measurable or evaluable disease are included in the analysis.		

BICR = blinded independent central review; CBR = clinical benefit rate; CCOD = clinical cutoff date; CR = complete response; CSR = clinical study report; DOR = duration of response; ECOD = enrolment cutoff date; NG = nasogastric; NSCLC = non-small cell lung cancer; PFS = progression-free survival; PO = orally; PR = partial response; ORR = objective response rate; OS= overall survival; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumours; TTR = time to response.

2.5.6. Discussion on clinical efficacy

The MAH of Rozlytrek requested two site and histology independent extensions of indication in paediatric patients:

1) NTRK fusion positive solid tumours with no satisfactory treatment options in paediatric patients from birth to 12 years.

2) ROS1 fusion positive solid tumours with no satisfactory treatment options in paediatric patients from birth to 18 years.

Regarding the indication in NTRK fusion positive solid tumours, Rozlytrek was already authorised in adolescent (12-18 years) and adult patients in 2019 under CMA. The SOBs collecting additional clinical and molecular data are ongoing with due date March 2027. At the time of the initial MAA, the available paediatric efficacy data for the NTRK indication included 7 paediatric patients aged from 4 months to 9 years. Although no efficacy data for entrectinib in NTRK solid tumour were available in adolescent, the CHMP concluded that the PK simulations performed for adolescents within BSA 1.1-1.5 m^2 showed that the exposure was within those obtained in adults, and that the activity of entrectinib in adolescent was considered established based on extrapolation of data obtained in adult patients with NTRK fusion positive solid tumours, so as to grant the indication to adolescent (12-18) in addition to adults. Further, no age-specific drug formulation was yet available to administer drug in paediatric subjects.

Regarding the indication in ROS1 fusion positive solid tumours, Rozlytrek is currently authorised only in ROS1 positive NSCLC in adults, therefore entrectinib (or other drugs) does not hold a site and histology independent indication based on ROS1 biomarker. Of note, no scientific advice has been requested for ROS1 positive solid tumour indication in paediatrics, which was also never discussed with PDCO/in the PIP.

Design and conduct of clinical studies

For the two sought indications, the MAH submitted two separate datasets (one for NTRK and one for ROS1 indication) obtained by pooling the available paediatric data from 3 Phase I/II trials: **STARTRK-NG** (where most of the patients were recruited), **TAPISTRY** and **STARTRK-02**. Data from the three studies above were pooled due to the rarity of paediatric patients with NTRK/ROS1 fusion-positive tumours and the small sample sizes of patients <18 years, as those studies had similar patient populations, dosing regimens, and efficacy endpoints. This is acceptable, although from a statistical perspective the entire programme is mostly exploratory rather than confirmatory.

STARTRK-NG is a Phase I/II open-label, dose escalation and expansion study for entrectinib in paediatric patients with locally advanced or metastatic solid or primary CNS tumours. Overall, a total of 68 patients were enrolled in this trial. The dose escalation phase aimed at MTD/DLT assessment in children. The initial paediatric MTD-based RP2D was 550 mg/m^2, however, based on matching paediatric to adult exposures, a dose of 300 mg/m^2 using the capsule formulation (F06) was subsequently recommended for ≥6 months age children who can swallow capsules. The dose expansion phase was extensively revised based on accumulating knowledge on entrectinib. The most recent study design includes two cohorts B and D including

paediatric patients with, respectively, primary brain and extracranial solid tumours progressed to or with no acceptable standard therapy and harbouring either NTRK or ROS1 fusion. The evaluation of entrectinib activity in terms of ORR was the primary objective of the dose expansion phase. While sample size was calculated for the two cohorts, an integrated efficacy analysis was planned based however on the molecular alterations (NTRK or ROS1) and not on the site of the primary tumour intra or extracranial.

A minority of paediatric patients were included in other two supportive studies. TAPISTRY is a Phase II, global, multicenter, open-label, multi-cohort platform study. In this study, Cohort A and B are enrolling patients receiving entrectinib with unresectable, locally advanced or metastatic solid tumours harbouring ROS1 and NTRK1/2/3 fusions, respectively. STARTRK-02 is the main phase II study for entrectinib in adult patients. Under the previous sponsor, two adolescents with ROS1 fusion positive tumours were enrolled which have been included in the ROS1 pooled analysis.

NTRK and ROS1 positivity were assessed by means of different nucleic acid-based assays. The current wording in section 4.2 of the SmPC on patient selection (that a validated assay is required, and that NTRK gene fusion positive status must be established prior to start Rozlytrek) is acceptable.

Efficacy data and additional analyses

NTRK indication

The updated integrated efficacy analysis supporting the extension of the NTRK indication is based on a total of 44 paediatric patients with NTRK fusion-positive tumours, both primary CNS and extracranial, pooled from the STARTRK-NG (n=34) and TAPISTRY (n=10) studies. Specifically, 38 patients were <12 years (adolescents ≥12 years are already included in the indication). All paediatric patients included in the pooled dataset had tumours that harbour an NTRK gene fusion with no evidence of co-occurrent mutations, not previously treated with TRK inhibitors, with measurable or evaluable disease at baseline, who received at least 1 dose of entrectinib and had at least 6 months of follow-up at the updated cut-off date (CCOD) of 16 July 2023 (i.e. enrolled before 16 January 2023).

For the pooled analysis, the primary endpoint was ORR as assessed by BICR according to RECIST 1.1 for solid tumours or RANO criteria for primary CNS solid tumours, based on confirmed responses by a ≥4 weeks assessment. DOR was secondary endpoint, together with TTR, CBR, PFS and OS. ORR is considered an acceptable endpoint in the context of non-controlled single arm data to evaluate drug activity, complemented by DOR. The review by independent reviewer is also supported. Quality issues with a BCR reader were identified during the procedure, however a process of re-reading of tumour scans was appropriately conducted, thus not raising concern. The interpretation of time-related endpoints PFS and OS is generally hampered by the single arm design, and by the fact that the dataset includes different tumour types that may have different natural history/prognosis.

Overall, updated results for 44 patients were consistent and confirmed the data seen in the pooled analysis including 33 NTRK patients initially submitted. At the updated CCOD, the median duration of survival follow-up was 24 months, and the median duration of treatment with entrectinib was 18.4 months. More than half of the patients (23/44) are still taking entrectinib, with PD being the most common reason for treatment discontinuation. Patient had a median age at enrolment of 4 years, ranging from 1.3 months to 15 years. Most of them were white with good performance status. Approximately half (20/44) had a primary CNS tumour, while patients with extracranial solid tumour had mostly sarcoma (21/44) plus 1 patient each with melanoma, papillary thyroid cancer and kidney cancer. In more detail, various CNS tumour types were

included (glioma, glioblastoma, ganglioglioma, glioneural, astrocytoma, medulloblastoma), while the two mostly represented sarcoma were infantile fibrosarcoma (11) and spindle cell sarcoma (8). Considering the sought indication in a "last line" setting, the MAH was requested to discuss the quite relevant number of patients with locally advanced disease (76%) and non-pretreated (>30%) in the efficacy NTRK paediatric dataset. For primary CNS tumours, the prevalence of locally advanced disease is considered in line with literature data reporting low metastatic spread outside CNS[33] [34]. Also, for patients with no CNS-primary tumours, in literature infantile fibrosarcomas are considered tumours with low malignant potential that are rarely metastasizing[35], while spindle cell sarcoma includes entities that recur locally, with apparently no metastatic potential, and others that behave aggressively often featuring distant spread[36]. With regard to prior treatment, the MAH clarified that only 9/44 (20%) patients have not received any kind of prior treatment, as there were 10 patients who had received surgery and/or RT as prior treatment. ORR was similar in those patients with no prior treatment (4/7, 57%), thus ORR does not seem to be driven by patients in 1st line treatment. Therefore, the NTRK updated paediatric efficacy dataset can be considered overall reflective of the sought indication in terms of composition with regard to locally advanced tumours and prior treatment.

In the NTRK integrated efficacy dataset, the overall ORR was 72.7% (32/44) 95%CI 57.21, 85.04, with a high rate of CR (45.5%, which seems rather unusual for a last line setting), and 27.3% of PR. Only two patients, both with primary CNS tumours, had progressive disease as their best response. The overall ORR in the paediatric dataset is comparable to the ORR of 61.3% (95%CI 53, 69.2) shown by entrectinib in the adult setting (n=150). Only patients with CNS primary tumours had prior RT treatment (8 out of 19), of those 1 was treated with RT<2 months before starting entrectinib, and achieved intracranial CR, while the other were treated > 3 months before and one received RT even >9 years before. Overall, in patients with primary CNS tumours, confirmed objective responses were achieved in 5/8 patients (62.5%; 95% CI 24.5, 91.5) who received RT, and in 5/12 patients who did not receive RT (41.7%), thus no evidence suggests that prior RT had an impact on the ORR.

Tumour responses overall occurred quite early during the treatment (median TTR <2 months) and overall appears durable, with median BICR-assessed confirmed DOR for responders not reached (95% CI: 25.4 months, NE). For comparison, median DOR in the adult dataset was 20 months (95%CI 13.2, 31.1).

When analysed by tumour type, responses were observed both in patients with primary CNS (10/20, ORR 50%, 95%CI 27, 72.8), although higher ORR was recorded in extracranial solid tumours (22/24, ORR 91.7%); in details infantile fibrosarcoma 90.9% (10/11), spindle cell sarcoma 100% (8/8), complete response was recorded in 1 patient each with melanoma, papillary thyroid cancer and kidney cancer.

When analysed by age, responses were seen across all age subgroups analysed: 2 months - <2 years ORR 64.3% (9/14); 2-12 years ORR 79.2% (19/24); 12-18 years ORR 66.7% (4/6). More granular evaluation of efficacy by age showed 8/10 (80%) responding patients in the 0-6 months range, while only 2/6 (33.3%) responded in the 6 months-2 years range. However, among the non-responding patients, two subjects with CNS primary tumours and non-target lesions/non-measurable disease only (categorized as SD) had however

[33] Chamdine O, Broniscer A, Wu S, et al. Metastatic low-grade gliomas in children: 20 years' experience at St. Jude Children's Research Hospital. Pediatr Blood Cancer. 2016;63:62-70.
[34] Fangusaro J. Pediatric high grade glioma: a review and update on tumour clinical characteristics and biology. Front Oncol. 2012;2:105.
[35] Ferrari A, Brennan B, Casanova M, et al. Pediatric non-rhabdomyosarcoma soft tissue sarcomas: standard of care and treatment recommendations from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). Cancer Manag Res. 2022;14:2885-2902.
[36] Sbaraglia M, Bellan E, Dei Tos AP. The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives. Pathologica. 2021 Apr;113(2):70-84.

BICR-assessed CR of their non-target lesions. Therefore, based on this additional information, in the age range 6 months-2 years entrectinib still show antitumor activity (i.e. at least 3 patients out of 6 with tumour reduction) overall similar to younger as well as older subjects. Over 2 years up to 6 years of age, entrectinib showed clinical activity with 12/15 patients responding. Efficacy, although in a limited dataset of patients, demonstrated a quite consistent response, across age groups as well as compared to the larger dataset of adults/adolescents.

Median PFS was NE (95% CI: 23.1, NE) and median OS was NE (95% CI: 35.7, NE). PFS and OS are of difficult interpretation due to the size and type of dataset as well as the single arm design.

In order to further support the extension of NTRK indication, data from a Compassionate use programme were reported, where 12 out of 13 paediatric patients (<12 years of age) with NTRK fusion positive solid tumours responded to entrectinib. This data can be considered supportive, although no details on the methodology of tumour assessment and collection of this data are available.

In addition, a natural history study (included in the PIP) was carried out by the MAH with the aim to characterize the natural history of NTRK gene fusion positive solid tumours in paediatric patients treated with historical standard of care (non-targeted) therapies (data not shown). In the CNSonTRK dataset it seems that a decreased real world ORR was observed among patients treated with non-targeted therapy in later lines. Less clear are the data regarding chemotherapy in the CHOP and literature review data sources. It is of note that in some cases NTRK inhibitors have been used in apparently earlier settings such as neoadjuvant. The effort of contextualizing data for NTRK fusion positive solid tumours in children is appreciated, however data are not easily interpretable, and the limits of this analysis are acknowledged.

ROS1 indication

The updated integrated efficacy analysis supporting an indication for entrectinib in paediatric patients with ROS1 fusion positive solid tumours with no satisfactory treatment option is based on a total of **19 paediatric patients** with ROS1 fusion-positive tumours, both primary CNS and extracranial, pooled from the STARTRK-NG (n=16), STARTRK-01 (n=2) and TAPISTRY (n=1) studies. All paediatric patients included in the pooled dataset had tumours that harbour a ROS1 gene fusion with no evidence of co-occurrent mutations, not previously treated with ROS1 inhibitors, with measurable or evaluable disease at baseline, who received at least 1 dose of entrectinib and had at least 6 months of follow-up at the cut-off date (CCOD) of 8 March 2023 (i.e. enrolled up to 8 September 2022).

Overall, 3 patients had less than 2 years (minimum age 3 months), most were in the age range 2-12 years (n=13), and 3 subjects had over 12 years of age (maximum 15 years). Median age at enrolment was 8 years. There was the same number of male and female, mostly White and with good performance status. Overall, most patients had sarcoma (10), of those 7 with inflammatory myofibroblastic tumour), and 8 patients had primary CNS tumours (42.1%, including different type of tumours), and one a NSCLC. More than 80% were classified as locally advanced tumours, and up to 60% of patients have not received any prior systemic treatment. In this regard, the MAH was requested to discuss the representativeness of the dataset taking into account the sought "last line" indication. While the prevalence of patients with locally advanced tumours seems in line with literature data for CNS tumours as well as for IMT (see also discussion on NTRK

above[37] [38] [39] [40]), some doubt still remains over the high number of patients with no prior treatment (higher than the NTRK dataset), acknowledging the lack of SoC in some diseases. In addition, in tumour types that can be more indolent (e.g., IMT, infantile fibrosarcoma, low-grade glioma) the importance of the uncertainties in the evaluation of the B/R balance, including potential long term safety concerns, could not be established in the overall population. Further, also duration of response is of more difficult evaluation in the context of per se indolent diseases.

In the updated ROS1 integrated efficacy dataset, the overall ORR was 63.2% (12/19) (38.36, 83.71), almost same as the prior data cut off (62.5%), with 3 patients achieving CR (15.8%). Large confidence interval due to the low number of patients is noted. Stable disease was recorded in 31.6% of the patients. However, for some of the tumours included (e.g. inflammatory myofibroblastic tumour) known to have more indolent natural history it is hard to conclude whether the drug contributes to long disease stabilization or not. None of the patients experienced PD as best response, although the subject who was not evaluable for response (an adolescent with NSCLC) died after less than 2 months from progressive disease. Tumour responses overall occurred quite early during the treatment (median TTR <2 months) and median DOR for responders was not reached (95%CI 16.2-NE).

Regarding the site and histology independent indication sought in ROS1 positive paediatric solid tumours, the updated dataset is still of small sample size (n=19) and no new tumour types with ROS1 fusion were identified as compared to the previous dataset. As reported in the SmPC and EPAR for entrectinib (and larotrectinib) in NTRK setting, "The extent to which tissue of origin and concomitant genetic alterations are effect modifiers, is not completely understood." Though it is acknowledged that entrectinib appears active in the provided dataset, and it is also acknowledged the apparent rarity of the ROS1 fusion alteration in paediatric solid tumours (0.5% overall), the overall sample size (n=19) is too limited to conclude that the data represent clinical benefit across a site and histology independent target population including very different tumour types with very different natural histories. Further, there is no ROS1 "agnostic" indication in adults for entrectinib (nor for any other targeted drugs) that can provide support and could serve as a bridge to the proposed paediatric indication. As such, the ROS1 fusion-positive paediatric solid tumours indication was no longer pursued.

Additional efficacy data needed in the context of a conditional MA:

The clinical data supporting this extension of indication cannot be considered comprehensive at the time of approval as duration of response is not fully characterised in the context of a single arm trial, number of patients is limited and the adult and adolescent dataset from which extrapolation could be performed remains under conditional approval.

The ongoing SOBs imposed in the context of the initial MA were the following :

- 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

[37] Chamdine O, Broniscer A, Wu S, et al. Metastatic low-grade gliomas in children: 20 years' experience at St. Jude Children's Research Hospital. Pediatr Blood Cancer. 2016;63:62-70.
[38] Fangusaro J. Pediatric high grade glioma: a review and update on tumour clinical characteristics and biology. Front Oncol. 2012;2:105.
[39] Ferrari A, Brennan B, Casanova M, et al. Pediatric non-rhabdomyosarcoma soft tissue sarcomas: standard of care and treatment recommendations from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). Cancer Manag Res. 2022;14:2885-2902.
[40] Casanova M, Brennan B, Alaggio R, et al. Inflammatory myofibroblastic tumour: the experience of the European paediatric Soft Tissue Sarcoma Study Group (EpSSG). Eur J Cancer. 2020;127:123-129.

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.

- In order to further investigate the impact of the presence/absence of other molecular alteration on the efficacy of entrectinib, the MAH should submit the results from tumour genomic profiling by plasma and/or tissue when possible at baseline and progression together with clinical outcomes association per tumour histology for the patients from the updated pooled analysis.

These SOBs will allow to provide comprehensive data also for the new NTRK paediatric (<12 years of age) indication. Based on current enrolment projections, it is estimated that the paediatric NTRK efficacy database at the due date for the existing SOB#1 will comprise a total of approximately 64 patients aged <18 years old (i.e. additional 20 patients) with at least 6 months of follow-up, of whom 49 with less than 12 years of age. No amendment to the current SOB is needed.

2.5.7. Conclusions on the clinical efficacy

To support the extension of the site and histology independent **NTRK** fusion positive solid tumours indication of entrectinib in paediatric patients <12 years with no satisfactory treatment options, an updated pooled analysis of n=44 paediatric subjects with mixed tumour types was presented. Although higher ORR was recorded in extracranial solid tumours, responses were seen also in CNS primary cancers. Noting all the limits of an uncontrolled and exploratory dataset, the already approved NTRK indication in adolescent and adults is considered supportive of an extrapolation to lower ages, considering also the similar activity of entrectinib observed in terms of ORR and DOR between the adults and paediatrics pooled datasets, as well as across various age ranges when analysed more granularly.

During the procedure, the MAH did not further pursue the ROS1 fusion-positive paediatric solid tumours indication.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- 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. The results should be submitted by 31 March 2027.

- In order to further investigate the impact of the presence/absence of other molecular alteration on the efficacy of entrectinib, the MAH should submit the results from tumour genomic profiling by plasma and/or tissue when possible at baseline and progression together with clinical outcomes association per tumour histology for the patients from the updated pooled analysis. The results should be submitted by

31 March 2027.

2.5.8. Clinical safety

The MAH in support of the safety profile of entrectinib in the sought extension of indication has submitted safety data coming from three ongoing studies: STARTRK-NG (n = 68), TAPISTRY (n = 21), and STARTRK-02 (n = 2) which were pooled and analysed collectively as **integrated safety population (n = 91) with a clinical cutoff date (CCOD) of 16 July 2023.**

The pooled analysis includes subjects regardless of the formulation, dosing regimen, and duration of treatment received by the patients. Data are also presented by study.

Of the 91 paediatric patients in the integrated dataset, 21 are infants (0 to <2 years), 55 are children (≥ 2 to <12 years), and 15 are adolescents (≥ 12 to <18 years).

Baseline characteristics: 51% were female, 49% were male, and the majority were White (63%). The median age was 6.0 years (range: 0–17 years), and the majority of patients (60%) were ≥ 24 months to < 12 years old. The youngest patient at enrolment was 1.3 months old. The majority of patients 76% had a Karnofsky/Lansky performance score of at least 90 at screening.

54.9% had an NTRK altered kinase and 25.3% had a ROS1 altered kinase. The median time from diagnosis to start of treatment was 5.6 months (range: 0.3–164.7 months).

At baseline, the majority of patients (71.9%) presented with locally advanced disease, while 28.1% of patients presented with metastatic disease.

60.4% received previous systemic cancer therapy. The majority of patients (54.9%) received a chemotherapy treatment, 15 patients (16.5%) received immunotherapy, 15 patients (16.5%) received targeted therapy, and 14 patients (15.4%) received other treatments. Twenty-eight patients (30.8%) received radiotherapy, and 52 patients (57.1%) underwent surgery prior to study enrolment.

Table 42 : Summary of Studies Contributing to Safety Evaluation

Study Number	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cutoff Date
STARTRK-NG (CO40778)	Phase I/II open-label, dose escalation, and expansion	Paediatric patients with locally advanced or metastatic solid or primary CNS tumours	68	**Phase I:** Doses 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	16 July 2023

TAPISTRY (BO41932)	Phase II, global, multicenter, open-label	Paediatric patients with *NTRK* or *ROS1* fusion-positive tumours	21	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	16 July 2023
STARTRK-02 (GO40782)	Phase II, global, multicenter, open-label	Paediatric patients with locally advanced or metastatic solid tumours that harbour *ROS1* gene rearrangement [a]	2	600 mg PO daily	16 July 2023

2.5.8.1. Patient exposure

At the CCOD (16 July 2023), of the 91 enrolled patients, 63 patients (69.2%) remained on study, and 28 patients (30.8%) had withdrawn from the study.

Table 43: Study treatment exposure

Study Treatment Exposure, Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782, GO40783, GO40784

	NTRK-Adult (N=326)	ROS1 NSCLC-Adult (N=247)	Other-Adult (N=189)	Total-Adult (N=762)	Pediatric (N=91)	Total (N=853)
Treatment duration (months)						
n	324	247	189	760	91	851
Mean (SD)	15.69 (17.31)	20.83 (19.31)	8.03 (13.85)	15.46 (17.86)	14.02 (11.97)	15.30 (17.33)
Median	10.10	14.16	2.63	8.28	11.07	8.57
Min - Max	0.0 - 83.5	0.0 - 86.3	0.0 - 75.8	0.0 - 86.3	0.1 - 56.0	0.0 - 86.3
Total cumulative dose (mg)						
n	325	247	189	761	91	852
Mean (SD)	223792.07 (252902.35)	303462.55 (293365.63)	126571.41 (219269.52)	225505.48 (267260.35)	126492.12 (141221.01)	214930.11 (258525.83)
Median	137400.00	184600.00	43600.00	117600.00	73500.00	115700.00
Min - Max	600.0 - 1374000.0	600.0 - 1411600.0	200.0 - 1338000.0	200.0 - 1411600.0	1779.3 - 834800.0	200.0 - 1411600.0
Dose intensity (%) (with respect to total dose)						
n	324	247	189	760	91	851
Mean (SD)	81.49 (24.38)	80.59 (22.18)	90.37 (32.03)	83.41 (26.13)	105.53 (41.36)	85.77 (28.94)
Median	92.31	88.20	96.88	92.64	100.00	94.64
Min - Max	11.6 - 260.0	17.4 - 133.3	24.5 - 388.3	11.6 - 388.3	28.8 - 387.3	11.6 - 388.3
Dose intensity (%) (with respect to total number of doses)						
n	259	247	174	680	70	750
Mean (SD)	92.44 (13.14)	93.68 (12.15)	95.00 (9.45)	93.54 (11.95)	95.87 (6.88)	93.76 (11.59)
Median	97.14	98.02	100.00	98.16	98.29	98.18
Min - Max	14.2 - 100.0	17.4 - 101.6	43.3 - 100.0	14.2 - 101.6	65.6 - 100.0	14.2 - 101.6
Number of doses						
n	259	247	174	680	70	750
Mean (SD)	510.2 (549.4)	610.5 (572.9)	231.8 (421.4)	475.4 (548.8)	467.4 (369.8)	474.6 (534.4)
Median	310.0	414.0	68.0	251.0	476.0	273.5
Min - Max	1 - 2400	1 - 2553	1 - 2280	1 - 2553	6 - 1628	1 - 2553
Missed doses						
n	259	247	174	680	70	750
At least one missed dose	205 (79.2%)	196 (79.4%)	80 (46.0%)	481 (70.7%)	42 (60.0%)	523 (69.7%)
Total number of missed doses						
n	259	247	174	680	70	750
Mean (SD)	24.53 (44.60)	20.85 (34.69)	8.97 (19.66)	19.21 (36.45)	19.17 (36.00)	19.21 (36.39)
Median	8.00	9.00	0.00	5.00	4.00	5.00
Min - Max	0.0 - 458.0	0.0 - 383.0	0.0 - 128.0	0.0 - 458.0	0.0 - 210.0	0.0 - 458.0

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

CCOD: Jul 16 2023, DBL: Nov 18 2019 (GO40783), Oct 20 2020 (GO40784), Sep 7 2023 (CO40778, BO41932, GO40782)

Program: root/clinical_studies/RO7102122/share/pool_EMA_2023/prod/program/t_ex_mis.sas / Output: root/clinical_studies/RO7102122/share/pool_EMA_2023/prod/output/t_ex_mis_SE_SCS.out
05OCT2023 13:02 Page 1 of 1

Based on the July 2023 CCOD, the median of duration of exposure was 11.1 months (range: 0.1-56.0 months) for the paediatric subgroups.

Table 44: Duration of exposure in the 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)

2.5.8.2. Adverse events

Table 45: summary of adverse events

Safety Summary, Safety-Evaluable Patients
Protocols: GO40782, GO40783, GO40784, CO40778, BO41932

	NTRK-Adult (N=326)	ROS1 NSCLC-Adult (N=247)	Other-Adult (N=189)	Total-Adult (N=762)	Pediatric (N=91)	Total (N=853)
Patients With AE	325 (99.7%)	247 (100%)	185 (97.9%)	757 (99.3%)	90 (98.9%)	847 (99.3%)
Patients With Related AE	298 (91.4%)	234 (94.7%)	169 (89.4%)	701 (92.0%)	81 (89.0%)	782 (91.7%)
Patients With Serious AE	148 (45.4%)	115 (46.6%)	74 (39.2%)	337 (44.2%)	45 (49.5%)	382 (44.8%)
Patients With Related Serious AE	52 (16.0%)	41 (16.6%)	13 (6.9%)	106 (13.9%)	15 (16.5%)	121 (14.2%)
Patients with NCI-CTCAE >= Grade 3 AE	221 (67.8%)	180 (72.9%)	108 (57.1%)	509 (66.8%)	63 (69.2%)	572 (67.1%)
Patients with Related NCI-CTCAE >= Grade 3 AE	140 (42.9%)	113 (45.7%)	47 (24.9%)	300 (39.4%)	46 (50.5%)	346 (40.6%)
Patients with AE Leading to Discontinuation	48 (14.7%)	33 (13.4%)	16 (8.5%)	97 (12.7%)	11 (12.1%)	108 (12.7%)
Patients with Related AE Leading to Discontinuation	26 (8.0%)	17 (6.9%)	7 (3.7%)	50 (6.6%)	10 (11.0%)	60 (7.0%)
Patients with AE Leading to Dose Reduction	87 (26.7%)	86 (34.8%)	30 (15.9%)	203 (26.6%)	22 (24.2%)	225 (26.4%)
Patients with Related AE Leading to Dose Reduction	83 (25.5%)	85 (34.4%)	29 (15.3%)	197 (25.9%)	21 (23.1%)	218 (25.6%)
Patients with AE Leading to Dose Interruption	185 (56.7%)	127 (51.4%)	86 (45.5%)	398 (52.2%)	38 (41.8%)	436 (51.1%)
Patients with Related AE Leading to Dose Interruption	118 (36.2%)	86 (34.8%)	45 (23.8%)	249 (32.7%)	25 (27.5%)	274 (32.1%)
Patients with AE Leading to Death	25 (7.7%)	22 (8.9%)	7 (3.7%)	54 (7.1%)	0	54 (6.3%)

Investigator text for AEs encoded using MedDRA version 26.0.
Adult patients are defined as subjects >=18 years of age; Pediatric patients are defined as subjects <18 years of age.

CCOD: Jul 16 2023, DBL: Nov 18 2019 (GO40783), Oct 20 2020 (GO40784), Sep 7 2023 (CO40778, BO41932, GO40782)

Program: root/clinical_studies/RO7102122/share/pool_EMA_2023/prod/program/t_saf_sum.sas
Output: root/clinical_studies/RO7102122/share/pool_EMA_2023/prod/output/t_saf_sum_SE_ACO.out
05OCT2023 15:40

Page 1 of 1

Adverse Events

Almost all patients experienced at least one AE (90/91 patients, 98.9%).

AEs by SOC

The most frequent AEs by SOC (≥ 50% patients) were:

- Gastrointestinal disorders (76 patients [83.5%])
- Investigations (73 patients [80.2%])
- General disorders and administration site conditions (62 patients [68.1%])
- Infections and infestations (59 patients [64.8%])
- Respiratory, thoracic, and mediastinal disorders (54 patients [59.3%])
- Metabolism and nutrition disorders (52 patients [57.1%])
- Blood and lymphatic system disorders (46 patients [50.5%])

AEs by PT

Table 46: Frequent Adverse Events by Preferred Terms (≥10% of patients)

Adverse Events, with Incidence of at Least 10%, Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782, GO40783, GO40784

MedDRA System Organ Class MedDRA Preferred Term	NTRK-Adult (N=326)	ROS1 NSCLC-Adult (N=247)	Other-Adult (N=189)	Total-Adult (N=762)	Pediatric (N=91)	Total (N=853)
Total number of patients with at least one adverse event	325 (99.7%)	247 (100%)	185 (97.9%)	757 (99.3%)	90 (98.9%)	847 (99.3%)
Overall total number of events	6648	5845	3182	15675	2626	18301
GASTROINTESTINAL DISORDERS						
Total number of patients with at least one adverse event	251 (77.0%)	207 (83.8%)	150 (79.4%)	608 (79.8%)	76 (83.5%)	684 (80.2%)
Total number of events	910	875	571	2356	321	2677
CONSTIPATION	132 (40.5%)	129 (52.2%)	66 (34.9%)	327 (42.9%)	34 (37.4%)	361 (42.3%)
DIARRHOEA	129 (39.6%)	106 (42.9%)	52 (27.5%)	287 (37.7%)	36 (39.6%)	323 (37.9%)
NAUSEA	81 (24.8%)	85 (34.4%)	64 (33.9%)	230 (30.2%)	26 (28.6%)	256 (30.0%)
VOMITING	58 (17.8%)	65 (26.3%)	54 (28.6%)	177 (23.2%)	37 (40.7%)	214 (25.1%)
ABDOMINAL PAIN	37 (11.3%)	24 (9.7%)	20 (10.6%)	81 (10.6%)	18 (19.8%)	99 (11.6%)
DYSPHAGIA	32 (9.8%)	40 (16.2%)	19 (10.1%)	91 (11.9%)	0	91 (10.7%)
FLATULENCE	6 (1.8%)	10 (4.0%)	6 (3.2%)	22 (2.9%)	10 (11.0%)	32 (3.8%)
NERVOUS SYSTEM DISORDERS						
Total number of patients with at least one adverse event	252 (77.3%)	214 (86.6%)	149 (78.8%)	615 (80.7%)	45 (49.5%)	660 (77.4%)
Total number of events	818	788	468	2074	138	2212
DYSGEUSIA	117 (35.9%)	113 (45.7%)	67 (35.4%)	297 (39.0%)	8 (8.8%)	305 (35.8%)
DIZZINESS	111 (34.0%)	110 (44.5%)	53 (28.0%)	274 (36.0%)	8 (8.8%)	282 (33.1%)
PARAESTHESIA	42 (12.9%)	53 (21.5%)	39 (20.6%)	134 (17.6%)	2 (2.2%)	136 (15.9%)
HEADACHE	48 (14.7%)	44 (17.8%)	26 (13.8%)	118 (15.5%)	19 (20.9%)	137 (16.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Total number of patients with at least one adverse event	238 (73.0%)	190 (76.9%)	142 (75.1%)	570 (74.8%)	62 (68.1%)	632 (74.1%)
Total number of events	581	522	362	1465	218	1683
FATIGUE	99 (30.4%)	79 (32.0%)	75 (39.7%)	253 (33.2%)	25 (27.5%)	278 (32.6%)
OEDEMA PERIPHERAL	87 (26.7%)	85 (34.4%)	40 (21.2%)	212 (27.8%)	6 (6.6%)	218 (25.6%)
PYREXIA	57 (17.5%)	61 (24.7%)	39 (20.6%)	157 (20.6%)	46 (50.5%)	203 (23.8%)
ASTHENIA	47 (14.4%)	33 (13.4%)	33 (17.5%)	113 (14.8%)	2 (2.2%)	115 (13.5%)
INVESTIGATIONS						
Total number of patients with at least one adverse event	227 (69.6%)	179 (72.5%)	85 (45.0%)	491 (64.4%)	73 (80.2%)	564 (66.1%)
Total number of events	1110	811	267	2188	510	2698
WEIGHT INCREASED	123 (37.7%)	107 (43.3%)	26 (13.8%)	256 (33.6%)	35 (38.5%)	291 (34.1%)
BLOOD CREATININE INCREASED	122 (37.4%)	80 (32.4%)	37 (19.6%)	239 (31.4%)	30 (33.0%)	269 (31.5%)
ASPARTATE AMINOTRANSFERASE INCREASED	76 (23.3%)	50 (20.2%)	21 (11.1%)	147 (19.3%)	33 (36.3%)	180 (21.1%)
ALANINE AMINOTRANSFERASE INCREASED	73 (22.4%)	52 (21.1%)	16 (8.5%)	141 (18.5%)	31 (34.1%)	172 (20.2%)
NEUTROPHIL COUNT DECREASED	31 (9.5%)	27 (10.9%)	10 (5.3%)	68 (8.9%)	21 (23.1%)	89 (10.4%)
WHITE BLOOD CELL COUNT DECREASED	27 (8.3%)	20 (8.1%)	2 (1.1%)	49 (6.4%)	20 (22.0%)	69 (8.1%)
BLOOD ALKALINE PHOSPHATASE INCREASED	22 (6.7%)	9 (3.6%)	7 (3.7%)	38 (5.0%)	16 (17.6%)	54 (6.3%)

MedDRA System Organ Class MedDRA Preferred Term	NTRK-Adult (N=326)	ROS1 NSCLC-Adult (N=247)	Other-Adult (N=189)	Total-Adult (N=762)	Pediatric (N=91)	Total (N=853)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
Total number of patients with at least one adverse event	182 (55.8%)	156 (63.2%)	113 (59.8%)	451 (59.2%)	41 (45.1%)	492 (57.7%)
Total number of events	436	482	260	1178	106	1284
ARTHRALGIA	62 (19.0%)	68 (27.5%)	39 (20.6%)	169 (22.2%)	10 (11.0%)	179 (21.0%)
MYALGIA	66 (20.2%)	60 (24.3%)	36 (19.0%)	162 (21.3%)	6 (6.6%)	168 (19.7%)
PAIN IN EXTREMITY	44 (13.5%)	36 (14.6%)	15 (7.9%)	95 (12.5%)	21 (23.1%)	116 (13.6%)
BACK PAIN	31 (9.5%)	30 (12.1%)	26 (13.8%)	87 (11.4%)	8 (8.8%)	95 (11.1%)
MUSCULAR WEAKNESS	23 (7.1%)	37 (15.0%)	23 (12.2%)	83 (10.9%)	6 (6.6%)	89 (10.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Total number of patients with at least one adverse event	144 (44.2%)	157 (63.6%)	93 (49.2%)	394 (51.7%)	54 (59.3%)	448 (52.5%)
Total number of events	328	377	221	926	201	1127
DYSPNOEA	63 (19.3%)	79 (32.0%)	53 (28.0%)	195 (25.6%)	8 (8.8%)	203 (23.8%)
COUGH	54 (16.6%)	61 (24.7%)	31 (16.4%)	146 (19.2%)	34 (37.4%)	180 (21.1%)
OROPHARYNGEAL PAIN	15 (4.6%)	20 (8.1%)	9 (4.8%)	44 (5.8%)	12 (13.2%)	56 (6.6%)
NASAL CONGESTION	7 (2.1%)	7 (2.8%)	5 (2.6%)	19 (2.5%)	16 (17.6%)	35 (4.1%)
INFECTIONS AND INFESTATIONS						
Total number of patients with at least one adverse event	174 (53.4%)	145 (58.7%)	65 (34.4%)	384 (50.4%)	59 (64.8%)	443 (51.9%)
Total number of events	415	376	156	947	272	1219
URINARY TRACT INFECTION	54 (16.6%)	51 (20.6%)	11 (5.8%)	116 (15.2%)	18 (19.8%)	134 (15.7%)
UPPER RESPIRATORY TRACT INFECTION	24 (7.4%)	32 (13.0%)	11 (5.8%)	67 (8.8%)	28 (30.8%)	95 (11.1%)
PNEUMONIA	34 (10.4%)	26 (10.5%)	15 (7.9%)	75 (9.8%)	10 (11.0%)	85 (10.0%)
COVID-19	36 (11.0%)	11 (4.5%)	8 (4.2%)	55 (7.2%)	18 (19.8%)	73 (8.6%)
METABOLISM AND NUTRITION DISORDERS						
Total number of patients with at least one adverse event	169 (51.8%)	130 (52.6%)	85 (45.0%)	384 (50.4%)	52 (57.1%)	436 (51.1%)
Total number of events	584	411	255	1250	278	1528
HYPERURICAEMIA	56 (17.2%)	47 (19.0%)	12 (6.3%)	115 (15.1%)	3 (3.3%)	118 (13.8%)
DECREASED APPETITE	31 (9.5%)	34 (13.8%)	25 (13.2%)	90 (11.8%)	21 (23.1%)	111 (13.0%)
HYPERGLYCAEMIA	25 (7.7%)	15 (6.1%)	8 (4.2%)	48 (6.3%)	16 (17.6%)	64 (7.5%)
HYPERKALAEMIA	21 (6.4%)	17 (6.9%)	8 (4.2%)	46 (6.0%)	10 (11.0%)	56 (6.6%)
HYPERNATRAEMIA	13 (4.0%)	12 (4.9%)	4 (2.1%)	29 (3.8%)	14 (15.4%)	43 (5.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
Total number of patients with at least one adverse event	136 (41.7%)	91 (36.8%)	60 (31.7%)	287 (37.7%)	46 (50.5%)	333 (39.0%)
Total number of events	289	149	116	554	123	677
ANAEMIA	115 (35.3%)	78 (31.6%)	55 (29.1%)	248 (32.5%)	37 (40.7%)	285 (33.4%)
NEUTROPENIA	23 (7.1%)	11 (4.5%)	9 (4.8%)	43 (5.6%)	11 (12.1%)	54 (6.3%)

MedDRA System Organ Class MedDRA Preferred Term	NTRK-Adult (N=326)	ROS1 NSCLC-Adult (N=247)	Other-Adult (N=189)	Total-Adult (N=762)	Pediatric (N=91)	Total (N=853)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Total number of patients with at least one adverse event	105 (32.2%)	104 (42.1%)	54 (28.6%)	263 (34.5%)	39 (42.9%)	302 (35.4%)
Total number of events	191	203	90	484	88	572
RASH	25 (7.7%)	28 (11.3%)	10 (5.3%)	63 (8.3%)	10 (11.0%)	73 (8.6%)
PRURITUS	19 (5.8%)	25 (10.1%)	10 (5.3%)	54 (7.1%)	8 (8.8%)	62 (7.3%)
EYE DISORDERS						
Total number of patients with at least one adverse event	86 (26.4%)	79 (32.0%)	42 (22.2%)	207 (27.2%)	27 (29.7%)	234 (27.4%)
Total number of events	125	138	59	322	49	371
VISION BLURRED	29 (8.9%)	28 (11.3%)	15 (7.9%)	72 (9.4%)	5 (5.5%)	77 (9.0%)
VASCULAR DISORDERS						
Total number of patients with at least one adverse event	88 (27.0%)	86 (34.8%)	37 (19.6%)	211 (27.7%)	14 (15.4%)	225 (26.4%)
Total number of events	141	131	61	333	29	362
HYPOTENSION	47 (14.4%)	40 (16.2%)	23 (12.2%)	110 (14.4%)	6 (6.6%)	116 (13.6%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
Total number of patients with at least one adverse event	84 (25.8%)	68 (27.5%)	33 (17.5%)	185 (24.3%)	39 (42.9%)	224 (26.3%)
Total number of events	190	135	49	374	98	472
TIBIA FRACTURE	0	2 (0.8%)	0	2 (0.3%)	12 (13.2%)	14 (1.6%)
RENAL AND URINARY DISORDERS						
Total number of patients with at least one adverse event	83 (25.5%)	61 (24.7%)	45 (23.8%)	189 (24.8%)	32 (35.2%)	221 (25.9%)
Total number of events	151	116	80	347	62	409
HAEMATURIA	12 (3.7%)	13 (5.3%)	7 (3.7%)	32 (4.2%)	10 (11.0%)	42 (4.9%)

Investigator text for AEs encoded using MedDRA version 26.0.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For
frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Adult patients are defined as subjects >=18 years of age; Pediatric patients are defined as subjects <18 years of age.

CODD: Jul 16 2023, DBL: Nov 18 2019 (G040783), Oct 20 2020 (G040784), Sep 7 2023 (C040778, B041932, G040782)

Program: root/clinical_studies/RO7102122/share/pool_EMA_2023/prod/program/t_ae_inc.sas
Output: root/clinical_studies/RO7102122/share/pool_EMA_2023/prod/output/t_ae_inc_10P_SE_SCS.out
05OCT2023 13:19 Page 3 of 3
Adapted from t_ae_inc_10P_SE_SCS

AEs by intensity

There were no patients with Grade 5 AEs in the study.

A total of 63 patients (69.2%) experienced Grade 3–4 AEs. The most frequent Grade 3-4 AEs by SOC (≥20% of patients) were Investigations (31 patients [34.1%]) and Infections and infestations (22 patients [24.2%]).

The most frequent Grade 3 AEs related to entrectinib by PT (>= 4 patients) were weight increased (15 patients [16.5%]), neutrophil count decreased (9 patients [9.9%]) plus neutropenia (4 patients [4.4%]) and anaemia (4 patients [4.4%]). Grade 4 AEs related to entrectinib were reported in 5 patients (5.5%) and

included neutrophil count decreased (2 patients), pancreatitis, platelet count decreased, pneumonia, hypoxia, pulmonary oedema, respiratory failure, ALT increased, and AST increased (1 patient each).

Adverse Events Related to Treatment

89.0% experienced a treatment-related AEs

The most frequent AEs related to entrectinib **by SOC** (≥30% of patients) were:

- Investigations (68 patients [74.7%])
- Gastrointestinal disorders (49 patients [53.8%])
- Blood and lymphatic system disorders (35 patients [38.5%])
- Metabolism and nutrition disorders (33 patients [36.3%])
- Nervous system disorders (32 patients [35.2%])

The most frequent AEs related to entrectinib **by PT** (≥10% of patients) are shown below:

Table 47: Adverse Events related to study drug

Adverse Events Related to Study Drug, Safety-Evaluable Patients
Protocols: GO40782, GO40783, GO40784, CO40778, BO41932

MedDRA Preferred Term	NTRK-Adult (N=326)	ROS1 NSCLC-Adult (N=247)	Other-Adult (N=189)	Total-Adult (N=762)	Pediatric (N=91)	Total (N=853)
Total number of patients with at least one adverse event	298 (91.4%)	234 (94.7%)	169 (89.4%)	701 (92.0%)	81 (89.0%)	782 (91.7%)
Total number of events	3400	2882	1302	7584	992	8576
DYSGEUSIA	114 (35.0%)	106 (42.9%)	65 (34.4%)	285 (37.4%)	8 (8.8%)	293 (34.3%)
WEIGHT INCREASED	103 (31.6%)	95 (38.5%)	21 (11.1%)	219 (28.7%)	32 (35.2%)	251 (29.4%)
CONSTIPATION	96 (29.4%)	83 (33.6%)	26 (13.8%)	205 (26.9%)	23 (25.3%)	228 (26.7%)
DIARRHOEA	99 (30.4%)	81 (32.8%)	29 (15.3%)	209 (27.4%)	12 (13.2%)	221 (25.9%)
DIZZINESS	82 (25.2%)	87 (35.2%)	41 (21.7%)	210 (27.6%)	3 (3.3%)	213 (25.0%)
FATIGUE	80 (24.5%)	62 (25.1%)	53 (28.0%)	195 (25.6%)	15 (16.5%)	210 (24.6%)
BLOOD CREATININE INCREASED	100 (30.7%)	63 (25.5%)	21 (11.1%)	184 (24.1%)	24 (26.4%)	208 (24.4%)
ANAEMIA	72 (22.1%)	42 (17.0%)	22 (11.6%)	136 (17.8%)	29 (31.9%)	165 (19.3%)
NAUSEA	51 (15.6%)	51 (20.6%)	36 (19.0%)	138 (18.1%)	21 (23.1%)	159 (18.6%)
OEDEMA PERIPHERAL	57 (17.5%)	55 (22.3%)	18 (9.5%)	130 (17.1%)	2 (2.2%)	132 (15.5%)
ASPARTATE AMINOTRANSFERASE INCREASED	64 (19.6%)	38 (15.4%)	12 (6.3%)	114 (15.0%)	24 (26.4%)	138 (16.2%)
ALANINE AMINOTRANSFERASE INCREASED	56 (17.2%)	38 (15.4%)	12 (6.3%)	106 (13.9%)	22 (24.2%)	128 (15.0%)
MYALGIA	46 (14.1%)	40 (16.2%)	31 (16.4%)	117 (15.4%)	4 (4.4%)	121 (14.2%)
PARAESTHESIA	32 (9.8%)	47 (19.0%)	35 (18.5%)	114 (15.0%)	2 (2.2%)	116 (13.6%)
VOMITING	35 (10.7%)	40 (16.2%)	25 (13.2%)	100 (13.1%)	16 (17.6%)	116 (13.6%)
ARTHRALGIA	27 (8.3%)	31 (12.6%)	26 (13.8%)	84 (11.0%)	6 (6.6%)	90 (10.6%)
HYPERURICAEMIA	45 (13.8%)	32 (13.0%)	5 (2.6%)	82 (10.8%)	2 (2.2%)	84 (9.8%)
ASTHENIA	39 (12.0%)	19 (7.7%)	19 (10.1%)	77 (10.1%)	2 (2.2%)	79 (9.3%)
NEUTROPHIL COUNT DECREASED	28 (8.6%)	20 (8.1%)	9 (4.8%)	57 (7.5%)	19 (20.9%)	76 (8.9%)
MUSCULAR WEAKNESS	18 (5.5%)	18 (7.3%)	14 (7.4%)	50 (6.6%)	5 (5.5%)	55 (6.4%)
PERIPHERAL SENSORY NEUROPATHY	19 (5.8%)	21 (8.5%)	12 (6.3%)	52 (6.8%)	2 (2.2%)	54 (6.3%)
DYSPHAGIA	14 (4.3%)	28 (11.3%)	9 (4.8%)	51 (6.7%)	0	51 (6.0%)
HEADACHE	20 (6.1%)	14 (5.7%)	8 (4.2%)	42 (5.5%)	11 (12.1%)	53 (6.2%)
WHITE BLOOD CELL COUNT DECREASED	23 (7.1%)	14 (5.7%)	2 (1.1%)	39 (5.1%)	14 (15.4%)	53 (6.2%)
HYPERAESTHESIA	20 (6.1%)	15 (6.1%)	10 (5.3%)	45 (5.9%)	1 (1.1%)	46 (5.4%)
COGNITIVE DISORDER	17 (5.2%)	16 (6.5%)	12 (6.3%)	45 (5.9%)	0	45 (5.3%)
RASH	13 (4.0%)	21 (8.5%)	8 (4.2%)	42 (5.5%)	4 (4.4%)	46 (5.4%)
NEUROPATHY PERIPHERAL	23 (7.1%)	15 (6.1%)	6 (3.2%)	44 (5.8%)	0	44 (5.2%)
GAIT DISTURBANCE	15 (4.6%)	16 (6.5%)	12 (6.3%)	43 (5.6%)	1 (1.1%)	44 (5.2%)
DECREASED APPETITE	14 (4.3%)	13 (5.3%)	10 (5.3%)	37 (4.9%)	9 (9.9%)	46 (5.4%)
VISION BLURRED	19 (5.8%)	14 (5.7%)	8 (4.2%)	41 (5.4%)	3 (3.3%)	44 (5.2%)
NEUTROPENIA	19 (5.8%)	10 (4.0%)	7 (3.7%)	36 (4.7%)	10 (11.0%)	46 (5.4%)
HYPOTENSION	16 (4.9%)	17 (6.9%)	7 (3.7%)	40 (5.2%)	1 (1.1%)	41 (4.8%)
PRURITUS	11 (3.4%)	16 (6.5%)	6 (3.2%)	33 (4.3%)	3 (3.3%)	36 (4.2%)
DRY MOUTH	16 (4.9%)	8 (3.2%)	9 (4.8%)	33 (4.3%)	1 (1.1%)	34 (4.0%)
TASTE DISORDER	18 (5.5%)	8 (3.2%)	7 (3.7%)	33 (4.3%)	1 (1.1%)	34 (4.0%)
DYSPNOEA	17 (5.2%)	7 (2.8%)	8 (4.2%)	32 (4.2%)	2 (2.2%)	34 (4.0%)
PAIN IN EXTREMITY	13 (4.0%)	8 (3.2%)	7 (3.7%)	28 (3.7%)	7 (7.7%)	35 (4.1%)
BLOOD ALKALINE PHOSPHATASE INCREASED	12 (3.7%)	6 (2.4%)	4 (2.1%)	22 (2.9%)	13 (14.3%)	35 (4.1%)
MEMORY IMPAIRMENT	13 (4.0%)	15 (6.1%)	1 (0.5%)	29 (3.8%)	2 (2.2%)	31 (3.6%)
DRY SKIN	10 (3.1%)	16 (6.5%)	3 (1.6%)	29 (3.8%)	1 (1.1%)	30 (3.5%)
DISTURBANCE IN ATTENTION	10 (3.1%)	9 (3.6%)	9 (4.8%)	28 (3.7%)	2 (2.2%)	30 (3.5%)
BLOOD CREATINE PHOSPHOKINASE INCREASED	15 (4.6%)	12 (4.9%)	1 (0.5%)	28 (3.7%)	1 (1.1%)	29 (3.4%)
HYPERTRIGLYCERIDAEMIA	14 (4.3%)	13 (5.3%)	0	27 (3.5%)	2 (2.2%)	29 (3.4%)
CONFUSIONAL STATE	11 (3.4%)	9 (3.6%)	8 (4.2%)	28 (3.7%)	0	28 (3.3%)
VERTIGO	14 (4.3%)	9 (3.6%)	5 (2.6%)	28 (3.7%)	0	28 (3.3%)
ABDOMINAL PAIN	13 (4.0%)	6 (2.4%)	2 (1.1%)	21 (2.8%)	9 (9.9%)	30 (3.5%)
BALANCE DISORDER	9 (2.8%)	12 (4.9%)	6 (3.2%)	27 (3.5%)	0	27 (3.2%)
DYSPEPSIA	12 (3.7%)	6 (2.4%)	8 (4.2%)	26 (3.4%)	1 (1.1%)	27 (3.2%)
ATAXIA	9 (2.8%)	11 (4.5%)	5 (2.6%)	25 (3.3%)	2 (2.2%)	27 (3.2%)
HYPOAESTHESIA ORAL	9 (2.8%)	12 (4.9%)	5 (2.6%)	26 (3.4%)	0	26 (3.0%)
PHOTOPHOBIA	9 (2.8%)	9 (3.6%)	5 (2.6%)	23 (3.0%)	4 (4.4%)	27 (3.2%)
SOMNOLENCE	3 (0.9%)	10 (4.0%)	10 (5.3%)	23 (3.0%)	3 (3.3%)	26 (3.0%)
HYPOPHOSPHATAEMIA	12 (3.7%)	7 (2.8%)	3 (1.6%)	22 (2.9%)	3 (3.3%)	25 (2.9%)
PARAESTHESIA ORAL	6 (1.8%)	12 (4.9%)	6 (3.2%)	24 (3.1%)	0	24 (2.8%)
MUSCLE SPASMS	15 (4.6%)	4 (1.6%)	4 (2.1%)	23 (3.0%)	0	23 (2.7%)
OEDEMA	9 (2.8%)	11 (4.5%)	3 (1.6%)	23 (3.0%)	0	23 (2.7%)
ELECTROCARDIOGRAM QT PROLONGED	7 (2.1%)	9 (3.6%)	4 (2.1%)	20 (2.6%)	4 (4.4%)	24 (2.8%)
GASTROOESOPHAGEAL REFLUX DISEASE	8 (2.5%)	11 (4.5%)	3 (1.6%)	22 (2.9%)	1 (1.1%)	23 (2.7%)
PYREXIA	7 (2.1%)	13 (5.3%)	1 (0.5%)	21 (2.8%)	1 (1.1%)	22 (2.6%)
FALL	8 (2.5%)	8 (3.2%)	4 (2.1%)	20 (2.6%)	2 (2.2%)	22 (2.6%)
HYPERNATRAEMIA	7 (2.1%)	6 (2.4%)	2 (1.1%)	15 (2.0%)	8 (8.8%)	23 (2.7%)
LYMPHOCYTE COUNT DECREASED	6 (1.8%)	10 (4.0%)	1 (0.5%)	17 (2.2%)	5 (5.5%)	22 (2.6%)
FLATULENCE	3 (0.9%)	8 (3.2%)	4 (2.1%)	15 (2.0%)	7 (7.7%)	22 (2.6%)
HYPOAESTHESIA	7 (2.1%)	10 (4.0%)	2 (1.1%)	19 (2.5%)	0	19 (2.2%)
INCREASED APPETITE	5 (1.5%)	8 (3.2%)	2 (1.1%)	15 (2.0%)	6 (6.6%)	21 (2.5%)
URINARY INCONTINENCE	8 (2.5%)	5 (2.0%)	1 (0.5%)	14 (1.8%)	7 (7.7%)	21 (2.5%)
DYSAESTHESIA	9 (2.8%)	6 (2.4%)	2 (1.1%)	17 (2.2%)	2 (2.2%)	19 (2.2%)
MALAISE	8 (2.5%)	8 (3.2%)	2 (1.1%)	18 (2.4%)	0	18 (2.1%)
BLOOD UREA INCREASED	9 (2.8%)	6 (2.4%)	0	15 (2.0%)	4 (4.4%)	19 (2.2%)
PAIN OF SKIN	7 (2.1%)	8 (3.2%)	2 (1.1%)	17 (2.2%)	1 (1.1%)	18 (2.1%)
RASH MACULO-PAPULAR	5 (1.5%)	6 (2.4%)	6 (3.2%)	17 (2.2%)	1 (1.1%)	18 (2.1%)
BLOOD URIC ACID INCREASED	9 (2.8%)	6 (2.4%)	1 (0.5%)	16 (2.1%)	2 (2.2%)	18 (2.1%)
INSOMNIA	10 (3.1%)	4 (1.6%)	0	14 (1.8%)	5 (5.5%)	19 (2.2%)
PERIPHERAL SWELLING	8 (2.5%)	7 (2.8%)	1 (0.5%)	16 (2.1%)	2 (2.2%)	18 (2.1%)
ABDOMINAL DISTENSION	5 (1.5%)	8 (3.2%)	2 (1.1%)	15 (2.0%)	3 (3.3%)	18 (2.1%)
ABDOMINAL PAIN UPPER	8 (2.5%)	4 (1.6%)	2 (1.1%)	14 (1.8%)	3 (3.3%)	17 (2.0%)
AMNESIA	5 (1.5%)	8 (3.2%)	3 (1.6%)	16 (2.1%)	0	16 (1.9%)
PAIN	6 (1.8%)	7 (2.8%)	1 (0.5%)	14 (1.8%)	3 (3.3%)	17 (2.0%)
PHOTOSENSITIVITY REACTION	7 (2.1%)	4 (1.6%)	5 (2.6%)	16 (2.1%)	0	16 (1.9%)
HYPERGLYCAEMIA	7 (2.1%)	6 (2.4%)	0	13 (1.7%)	4 (4.4%)	17 (2.0%)
URINARY TRACT INFECTION	7 (2.1%)	5 (2.0%)	1 (0.5%)	13 (1.7%)	4 (4.4%)	17 (2.0%)
HYPERPHOSPHATAEMIA	9 (2.8%)	3 (1.2%)	0	12 (1.6%)	5 (5.5%)	17 (2.0%)
DYSARTHRIA	4 (1.2%)	9 (3.6%)	2 (1.1%)	15 (2.0%)	0	15 (1.8%)
GENERALISED OEDEMA	5 (1.5%)	5 (2.0%)	5 (2.6%)	15 (2.0%)	0	15 (1.8%)
STOMATITIS	5 (1.5%)	9 (3.6%)	1 (0.5%)	15 (2.0%)	0	15 (1.8%)
PLATELET COUNT DECREASED	6 (1.8%)	5 (2.0%)	1 (0.5%)	12 (1.6%)	4 (4.4%)	16 (1.9%)
LYMPHOPENIA	8 (2.5%)	1 (0.4%)	1 (0.5%)	10 (1.3%)	6 (6.6%)	16 (1.9%)
CARDIAC FAILURE	7 (2.1%)	5 (2.0%)	1 (0.5%)	13 (1.7%)	1 (1.1%)	14 (1.6%)
HYPERKALAEMIA	6 (1.8%)	4 (1.6%)	1 (0.5%)	11 (1.4%)	4 (4.4%)	15 (1.8%)
PNEUMONIA	7 (2.1%)	4 (1.6%)	2 (1.1%)	13 (1.7%)	1 (1.1%)	14 (1.6%)
BACK PAIN	5 (1.5%)	3 (1.2%)	4 (2.1%)	12 (1.6%)	2 (2.2%)	14 (1.6%)
OROPHARYNGEAL PAIN	5 (1.5%)	4 (1.6%)	3 (1.6%)	12 (1.6%)	2 (2.2%)	14 (1.6%)
SYNCOPE	8 (2.5%)	4 (1.6%)	0	12 (1.6%)	2 (2.2%)	14 (1.6%)
URINARY RETENTION	7 (2.1%)	2 (0.8%)	3 (1.6%)	12 (1.6%)	2 (2.2%)	14 (1.6%)
COUGH	6 (1.8%)	5 (2.0%)	0	11 (1.4%)	3 (3.3%)	14 (1.6%)
FACE OEDEMA	6 (1.8%)	4 (1.6%)	3 (1.6%)	13 (1.7%)	0	13 (1.5%)
HYPERCHOLESTEROLAEMIA	7 (2.1%)	6 (2.4%)	0	13 (1.7%)	0	13 (1.5%)
HYPOALBUMINAEMIA	6 (1.8%)	4 (1.6%)	1 (0.5%)	11 (1.4%)	3 (3.3%)	14 (1.6%)
HYPOKALAEMIA	3 (0.9%)	6 (2.4%)	2 (1.1%)	11 (1.4%)	3 (3.3%)	14 (1.6%)
BLOOD LACTATE DEHYDROGENASE INCREASED	9 (2.8%)	2 (0.8%)	1 (0.5%)	12 (1.6%)	1 (1.1%)	13 (1.5%)
EJECTION FRACTION DECREASED	6 (1.8%)	4 (1.6%)	2 (1.1%)	12 (1.6%)	1 (1.1%)	13 (1.5%)
ACUTE KIDNEY INJURY	7 (2.1%)	3 (1.2%)	2 (1.1%)	12 (1.6%)	0	12 (1.4%)
DEHYDRATION	6 (1.8%)	2 (0.8%)	3 (1.6%)	11 (1.4%)	1 (1.1%)	12 (1.4%)
HEPATIC FUNCTION ABNORMAL	5 (1.5%)	6 (2.4%)	0	11 (1.4%)	1 (1.1%)	12 (1.4%)
SINUS BRADYCARDIA	7 (2.1%)	4 (1.6%)	0	11 (1.4%)	1 (1.1%)	12 (1.4%)

MedDRA Preferred Term	NTRK-Adult (N=326)	ROS1 NSCLC-Adult (N=247)	Other-Adult (N=189)	Total-Adult (N=762)	Pediatric (N=91)	Total (N=853)
HYPOMAGNESAEMIA	6 (1.8%)	3 (1.2%)	1 (0.5%)	10 (1.3%)	2 (2.2%)	12 (1.4%)
BLOOD CHOLESTEROL INCREASED	3 (0.9%)	8 (3.2%)	0	11 (1.4%)	0	11 (1.3%)
DRY EYE	4 (1.2%)	7 (2.8%)	0	11 (1.4%)	0	11 (1.3%)
LEUKOPENIA	6 (1.8%)	1 (0.4%)	2 (1.1%)	9 (1.2%)	3 (3.3%)	12 (1.4%)
ORAL DYSAESTHESIA	3 (0.9%)	5 (2.0%)	3 (1.6%)	11 (1.4%)	0	11 (1.3%)
TREMOR	3 (0.9%)	5 (2.0%)	3 (1.6%)	11 (1.4%)	0	11 (1.3%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	5 (1.5%)	5 (2.0%)	0	10 (1.3%)	1 (1.1%)	11 (1.3%)
HYPONATRAEMIA	6 (1.8%)	1 (0.4%)	3 (1.6%)	10 (1.3%)	1 (1.1%)	11 (1.3%)
ORTHOSTATIC HYPOTENSION	4 (1.2%)	6 (2.4%)	0	10 (1.3%)	1 (1.1%)	11 (1.3%)
AGEUSIA	5 (1.5%)	4 (1.6%)	1 (0.5%)	10 (1.3%)	0	10 (1.2%)
DERMATITIS ACNEIFORM	0	6 (2.4%)	4 (2.1%)	10 (1.3%)	0	10 (1.2%)
HYPOCALCAEMIA	5 (1.5%)	1 (0.4%)	2 (1.1%)	8 (1.0%)	3 (3.3%)	11 (1.3%)
JOINT SWELLING	5 (1.5%)	4 (1.6%)	1 (0.5%)	10 (1.3%)	0	10 (1.2%)
OSTEOPOROSIS	4 (1.2%)	5 (2.0%)	1 (0.5%)	10 (1.3%)	0	10 (1.2%)
SKIN BURNING SENSATION	2 (0.6%)	3 (1.2%)	5 (2.6%)	10 (1.3%)	0	10 (1.2%)
BLOOD BILIRUBIN INCREASED	3 (0.9%)	4 (1.6%)	2 (1.1%)	9 (1.2%)	1 (1.1%)	10 (1.2%)
HAEMATURIA	3 (0.9%)	4 (1.6%)	0	7 (0.9%)	4 (4.4%)	11 (1.3%)
THROMBOCYTOPENIA	4 (1.2%)	1 (0.4%)	3 (1.6%)	8 (1.0%)	2 (2.2%)	10 (1.2%)
APHASIA	3 (0.9%)	5 (2.0%)	1 (0.5%)	9 (1.2%)	0	9 (1.1%)
GLOMERULAR FILTRATION RATE DECREASED	7 (2.1%)	2 (0.8%)	0	9 (1.2%)	0	9 (1.1%)
WEIGHT DECREASED	5 (1.5%)	4 (1.6%)	0	9 (1.2%)	0	9 (1.1%)
DYSURIA	0	4 (1.6%)	2 (1.1%)	6 (0.8%)	4 (4.4%)	10 (1.2%)
ALOPECIA	5 (1.5%)	3 (1.2%)	0	8 (1.0%)	0	8 (0.9%)
AMYLASE INCREASED	1 (0.3%)	5 (2.0%)	2 (1.1%)	8 (1.0%)	0	8 (0.9%)
DYSPHONIA	3 (0.9%)	5 (2.0%)	0	8 (1.0%)	0	8 (0.9%)
HYPOTHYROIDISM	6 (1.8%)	1 (0.4%)	1 (0.5%)	8 (1.0%)	0	8 (0.9%)
LOW DENSITY LIPOPROTEIN INCREASED	4 (1.2%)	4 (1.6%)	0	8 (1.0%)	0	8 (0.9%)
MUCOSAL INFLAMMATION	5 (1.5%)	2 (0.8%)	1 (0.5%)	8 (1.0%)	0	8 (0.9%)
TINNITUS	2 (0.6%)	5 (2.0%)	1 (0.5%)	8 (1.0%)	0	8 (0.9%)
TIBIA FRACTURE	0	1 (0.4%)	0	1 (0.1%)	10 (11.0%)	11 (1.3%)
PROTEINURIA	3 (0.9%)	3 (1.2%)	0	6 (0.8%)	2 (2.2%)	8 (0.9%)
BLOOD TRIGLYCERIDES INCREASED	0	6 (2.4%)	1 (0.5%)	7 (0.9%)	0	7 (0.8%)
HYPERTENSION	2 (0.6%)	5 (2.0%)	0	7 (0.9%)	0	7 (0.8%)
HYPERTRANSAMINASAEMIA	5 (1.5%)	1 (0.4%)	1 (0.5%)	7 (0.9%)	0	7 (0.8%)
LIPASE INCREASED	1 (0.3%)	2 (0.8%)	4 (2.1%)	7 (0.9%)	0	7 (0.8%)
NEURALGIA	3 (0.9%)	3 (1.2%)	1 (0.5%)	7 (0.9%)	0	7 (0.8%)
SKIN FISSURES	4 (1.2%)	3 (1.2%)	0	7 (0.9%)	0	7 (0.8%)
URTICARIA	2 (0.6%)	4 (1.6%)	1 (0.5%)	7 (0.9%)	0	7 (0.8%)
VISUAL IMPAIRMENT	4 (1.2%)	2 (0.8%)	1 (0.5%)	7 (0.9%)	0	7 (0.8%)
CHRONIC KIDNEY DISEASE	4 (1.2%)	2 (0.8%)	0	6 (0.8%)	1 (1.1%)	7 (0.8%)
ECZEMA	3 (0.9%)	3 (1.2%)	0	6 (0.8%)	1 (1.1%)	7 (0.8%)
HOT FLUSH	3 (0.9%)	2 (0.8%)	1 (0.5%)	6 (0.8%)	1 (1.1%)	7 (0.8%)
LEFT VENTRICULAR DYSFUNCTION	5 (1.5%)	0	1 (0.5%)	6 (0.8%)	1 (1.1%)	7 (0.8%)
OSTEOPENIA	3 (0.9%)	2 (0.8%)	1 (0.5%)	6 (0.8%)	1 (1.1%)	7 (0.8%)
FRACTURE	2 (0.6%)	3 (1.2%)	0	5 (0.7%)	2 (2.2%)	7 (0.8%)
ANXIETY	1 (0.3%)	3 (1.2%)	2 (1.1%)	6 (0.8%)	0	6 (0.7%)
BRAIN NATRIURETIC PEPTIDE INCREASED	4 (1.2%)	2 (0.8%)	0	6 (0.8%)	0	6 (0.7%)
DEPRESSION	2 (0.6%)	3 (1.2%)	1 (0.5%)	6 (0.8%)	0	6 (0.7%)
DIPLOPIA	2 (0.6%)	3 (1.2%)	1 (0.5%)	6 (0.8%)	0	6 (0.7%)
POLYNEUROPATHY	5 (1.5%)	1 (0.4%)	0	6 (0.8%)	0	6 (0.7%)
RENAL FAILURE	6 (1.8%)	0	0	6 (0.8%)	0	6 (0.7%)
RENAL IMPAIRMENT	3 (0.9%)	3 (1.2%)	0	6 (0.8%)	0	6 (0.7%)
SINUS ARRHYTHMIA	3 (0.9%)	3 (1.2%)	0	6 (0.8%)	0	6 (0.7%)
VISUAL ACUITY REDUCED	4 (1.2%)	2 (0.8%)	0	6 (0.8%)	0	6 (0.7%)

Investigator text for AEs encoded using MedDRA version 26.0. ** uncoded preferred term (if present) replaced by investigator text
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Adult patients are defined as subjects >=18 years of age; Pediatric patients are defined as subjects <18 years of age.

CCOD: Jul 16 2023, DBL: Nov 18 2019 (GO40783), Oct 20 2020 (GO40784), Sep 7 2023 (CO40778, BO41932, GO40782)

The combined list of AESIs for STARTRK-02, STARTRK-NG, and TAPISTRY include the following:

- **Bone fractures**
- **Cognitive disturbances**
- **Congestive cardiac failure**
- **QT prolongation**
- **Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law**
- **Suspected transmission of an infectious agent**

Bone fractures

A total of 27 out of 91 patients (29.7%) experienced a bone fracture event. Fourteen patients experienced more than one bone fracture event. Of the 14 patients with more than one bone fracture event, 6 patients experienced multiple fractures at the same time point. A majority of fractures occurred in patients < 12 years (24/27 patients).

Seventeen patients (18.7%) experienced a Grade 1-2 bone fracture. Ten patients (11.0%) experienced a Grade 3 bone fracture. There were no Grade 4 or 5 bone fracture events.

The majority of fractures occurred in the lower body. The most frequent bone fracture events by PT (≥5% of patients) were as follows:

- Tibia fracture (12 patients [13.2%])
- Femur fracture (5 patients [5.5%])
- Fibula fracture (5 patients [5.5%])

Severity: of the patients with a bone fracture event, 12 patients experienced a bone fracture that was serious (SAE). SAEs by PT included: femur fracture (5 patients), fracture and tibia fracture (2 patients each), limb fracture, lower limb fracture, pathological fracture, spinal compression fracture, and stress fracture (1 patient each). Bone fracture SAEs were assessed as related to entrectinib in 10 patients.

Six patients (6.6%) experienced bone fractures that led to treatment discontinuation. One patient (1.1%) experienced a bone fracture that led to dose reduction of entrectinib, and 5 patients (5.5%) experienced a bone fracture that led to dose interruption of entrectinib.

The median time to onset from first entrectinib dose was 4.30 months (range: 2.0–28.7 months).

Outcome: based on the medical review of individual patient data, as of the CCOD, a total of 23 patients had bone fracture events that were resolved, 1 patient had event that is resolving, and 4 patients had events that were resolved with sequelae. Four patients had bone fracture events that were not resolved as of the CCOD. One patient had bone fracture event that had an unknown outcome.

Some fractures have occurred in the setting of fall or other trauma. Among the 52 events of bone fracture, 17 events were reported as related to both entrectinib and external trauma, 24 events were reported as related to entrectinib alone, 8 events were reported as unrelated to entrectinib but related to external trauma, one event was reported as unrelated to both entrectinib and external trauma and for 2 events the relatedness to entrectinib/trauma is not known/not reported.

Of the 27 patients who reported a bone fracture 1 patient in the underweight category and 6 patients in the normal category had their BMI shifted to the overweight category post-baseline. One patient in the underweight category and 7 patients in the normal category had their BMI shifted to the obese category post-baseline.

Data submitted by the MAH regarding the interim report on risk fractures (including bone growth, density and biomarkers) does not allow to make sound conclusions due to limited available data. Likely the final report would be helpful in better characterizing the risk.

Machine-learning based methodology on entrectinib and bone fractures: the MAH has submitted a stepwise machine-learning based methodology in order to investigate the pathophysiological molecular mechanisms related to increased bone fracture risk, identification of measurable biomarkers and eventually selection of possible treatments.

Cardiovascular toxicity

- **Congestive cardiac failure**

Of the 91 patients in this expanded paediatric population, 5 patients (5.5%) experienced CHF events, of whom two patients experienced an event reported as Grade 1 (2.2%) and one patient each (1.1%) experienced events reported as Grade 2, Grade 3, or Grade 4. One patient (1.1%) experienced a CHF event

that was reported as serious with a Grade 4 pulmonary oedema which was assessed related to entrectinib. The patient was withdrawn from entrectinib and the event resolved.

Events of congestive heart failure by highest NCI CTCAE grade were 3 (any grade).

Table 48: Summary of Congestive heart failure events

Adverse Events by Highest NCI CTCAE Grade, System Organ Class and Preferred Term, Congestive Heart Failure, Safety-Evaluable Patients
Protocols: GO40782, GO40783, GO40784, CO40778, BO41932

MedDRA System Organ Class MedDRA Preferred Term Grade	NTRK-Adult (N=326)	ROS1 NSCLC-Adult (N=247)	Other-Adult (N=189)	Total-Adult (N=762)	Pediatric (N=91)	Total (N=853)
- Any adverse events -						
- Any Grade -	18 (5.5%)	16 (6.5%)	8 (4.2%)	42 (5.5%)	5 (5.5%)	47 (5.5%)
1	3 (0.9%)	2 (0.8%)	0	5 (0.7%)	2 (2.2%)	7 (0.8%)
2	8 (2.5%)	5 (2.0%)	4 (2.1%)	17 (2.2%)	1 (1.1%)	18 (2.1%)
1-2	11 (3.4%)	7 (2.8%)	4 (2.1%)	22 (2.9%)	3 (3.3%)	25 (2.9%)
3	7 (2.1%)	6 (2.4%)	4 (2.1%)	17 (2.2%)	1 (1.1%)	18 (2.1%)
4	0	1 (0.4%)	0	1 (0.1%)	1 (1.1%)	2 (0.2%)
3-4	7 (2.1%)	7 (2.8%)	4 (2.1%)	18 (2.4%)	2 (2.2%)	20 (2.3%)
5	0	2 (0.8%)	0	2 (0.3%)	0	2 (0.2%)
CARDIAC DISORDERS						
- Overall -						
- Any Grade -	9 (2.8%)	10 (4.0%)	4 (2.1%)	23 (3.0%)	2 (2.2%)	25 (2.9%)
1	2 (0.6%)	1 (0.4%)	0	3 (0.4%)	2 (2.2%)	5 (0.6%)
2	2 (0.6%)	2 (0.8%)	2 (1.1%)	6 (0.8%)	0	6 (0.7%)
1-2	4 (1.2%)	3 (1.2%)	2 (1.1%)	9 (1.2%)	2 (2.2%)	11 (1.3%)
3	5 (1.5%)	4 (1.6%)	2 (1.1%)	11 (1.4%)	0	11 (1.3%)
4	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
3-4	5 (1.5%)	5 (2.0%)	2 (1.1%)	12 (1.6%)	0	12 (1.4%)
5	0	2 (0.8%)	0	2 (0.3%)	0	2 (0.2%)

Investigator text for AEs encoded using MedDRA v26.0.
All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
Percentages are based on N in the column headings. AEs collected after first treatment dose are included.
Congestive Heart Failure composite terms: Acute Right Ventricular Failure, Cardiac Failure, Cardiac Failure Congestive, Cardiogenic Shock, Chronic Right Ventricular Failure, Ejection Fraction Decreased, Pulmonary Oedema.
Investigator text for AEs encoded using MedDRA v26.0.
All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
Percentages are based on N in the column headings. AEs collected after first treatment dose are included.
Adult patients are defined as subjects >=18 years of age; Pediatric patients are defined as subjects <18 years of age.

CCOD: Jul 16 2023, DBL: Nov 18 2019 (GO40783), Oct 20 2020 (GO40784), Sep 7 2023 (CO40778, BO41932, GO40782)

QT prolongation

Of the 91 patients in the expanded paediatric population as of a CCOD of 16 July 2023, 5 (5.5%) experienced QT prolongation events (any grade); 3 patients (3.3%) had Grade 1 events and two patients (2.2%) had Grade 2 events. No patients reported an event of QT interval prolongation Grade > 2. None of the QT prolongation events in this population was reported as serious or unresolved.

Neurologic AEs

Cognitive disturbances

Cognitive disorders include (cognitive disorder, confusional state, disturbance in attention, memory impairment, amnesia, mental status changes, hallucination, delirium, 'visual hallucination' and mental disorder).

A table summarizing cognitive disturbances is not available for the integrated safety dataset.

A total of 9 patients experienced an AE in the category of cognitive disorders of which 6 of grade 1, and 2 of grade 2 and 1 of grade 3. This patient experienced a Grade 3 mental status change which was assessed as

not serious and unrelated to entrectinib. This event led to dose interruption and has not resolved as of the CCOD. No cognitive disorders have been reported in the STARTRK-2 study.

Suspected transmission of an infectious agent

At the time of CCOD, no patients experienced suspected transmission of an infectious agent by the study treatment.

Drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law

At the time of CCOD, no patients reported any case of potential drug-induced liver injury that met Hy's Law criteria.

Other selected AEs

Changes in Weight

Overall, 35 patients (38.5%) reported weight increases during the study.

A total of 18 patients (19.8%) reported Grade 1-2 AEs of weight increased, of whom 17 patients had events related to entrectinib. Seventeen patients (18.7%) reported a Grade 3 AE of weight increased, of whom 15 patients had events related to entrectinib.

Two patients (2.2%) reported a Grade 2 and Grade 3 (one patient each) weight decrease unrelated to entrectinib during the study.

Adverse drug reactions

Adverse drug reactions (ADRs) that were assessed by the Sponsor as having a causal relationship to entrectinib were identified based on all AEs observed in the integrated safety population (i.e., all patients treated with entrectinib in the clinical studies STARTRK-NG, TAPISTRY, and STARTRK-02). ADRs were selected based on a frequency of $\geq 10\%$ for individual preferred terms or group of PTs pooled by medical concept. Less frequent events (i.e., $< 10\%$) could also be ADRs if supported by clinical experience, medical judgment, preclinical findings, or other data from the literature. A summary of ADRs in paediatric patients $<$ 18 years is presented in Table 49

Table 49 : Summary of Adverse Drug Reactions in Patients < 18 Years Treated with Entrectinib

Medical Concepts by Age Group, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782, GO40783, GO40784

Medical Concept MedDRA Preferred Term	Total (N=91)			
	Age Category			
	>= 28 days to < 24 months (N=21)	>= 24 months to < 12 years (N=55)	>= 12 years to < 18 years (N=15)	Total (N=91)
Total number of patients with at least one adverse event	21 (100%)	55 (100%)	14 (93.3%)	90 (98.9%)
Total number of events	333	854	152	1339
PYREXIA	13 (61.9%)	28 (50.9%)	5 (33.3%)	46 (50.5%)
ANAEMIA	13 (61.9%)	19 (34.5%)	5 (33.3%)	37 (40.7%)
VOMITING	10 (47.6%)	24 (43.6%)	3 (20.0%)	37 (40.7%)
DIARRHOEA	9 (42.9%)	24 (43.6%)	3 (20.0%)	36 (39.6%)
WEIGHT INCREASED	5 (23.8%)	22 (40.0%)	8 (53.3%)	35 (38.5%)
CONSTIPATION	9 (42.9%)	20 (36.4%)	5 (33.3%)	34 (37.4%)
COUGH	9 (42.9%)	22 (40.0%)	3 (20.0%)	34 (37.4%)
ASPARTATE AMINOTRANSFERASE INCREASED	9 (42.9%)	16 (29.1%)	8 (53.3%)	33 (36.3%)
ALANINE AMINOTRANSFERASE INCREASED	10 (47.6%)	14 (25.5%)	7 (46.7%)	31 (34.1%)
BLOOD CREATININE INCREASED	4 (19.0%)	19 (34.5%)	7 (46.7%)	30 (33.0%)
NEUTROPENIA [10]	10 (47.6%)	15 (27.3%)	5 (33.3%)	30 (33.0%)
FRACTURES [15]	2 (9.5%)	22 (40.0%)	3 (20.0%)	27 (29.7%)
FATIGUE [13]	1 (4.8%)	22 (40.0%)	3 (20.0%)	26 (28.6%)
NAUSEA	1 (4.8%)	19 (34.5%)	6 (40.0%)	26 (28.6%)
PAIN [7]	2 (9.5%)	17 (30.9%)	5 (33.3%)	24 (26.4%)
DECREASED APPETITIE	3 (14.3%)	16 (29.1%)	2 (13.3%)	21 (23.1%)
RASH [11]	8 (38.1%)	12 (21.8%)	0	20 (22.0%)
HEADACHE	0	18 (32.7%)	1 (6.7%)	19 (20.9%)
ABDOMINAL PAIN	2 (9.5%)	14 (25.5%)	2 (13.3%)	18 (19.8%)
URINARY TRACT INFECTION	5 (23.8%)	13 (23.6%)	0	18 (19.8%)
LUNG INFECTION [8]	6 (28.6%)	9 (16.4%)	1 (6.7%)	16 (17.6%)
MOOD DISORDERS [18]	2 (9.5%)	9 (16.4%)	2 (13.3%)	13 (14.3%)
URINARY RETENTION [16]	2 (9.5%)	10 (18.2%)	1 (6.7%)	13 (14.3%)
SLEEP DISTURBANCES [17]	2 (9.5%)	9 (16.4%)	1 (6.7%)	12 (13.2%)
ARTHRALGIA	0	9 (16.4%)	1 (6.7%)	10 (11.0%)
OEDEMA [6]	2 (9.5%)	8 (14.5%)	0	10 (11.0%)
COGNITIVE DISORDERS [1]	2 (9.5%)	5 (9.1%)	2 (13.3%)	9 (9.9%)
DEHYDRATION	1 (4.8%)	7 (12.7%)	0	8 (8.8%)
DIZZINESS [5]	0	8 (14.5%)	0	8 (8.8%)
DYSGEUSIA	0	5 (9.1%)	3 (20.0%)	8 (8.8%)
DYSPNOEA	1 (4.8%)	5 (9.1%)	2 (13.3%)	8 (8.8%)
ATAXIA [4]	1 (4.8%)	6 (10.9%)	0	7 (7.7%)
HYPOTENSION [14]	2 (9.5%)	4 (7.3%)	1 (6.7%)	7 (7.7%)
MUSCULAR WEAKNESS	0	4 (7.3%)	2 (13.3%)	6 (6.6%)
MYALGIA	0	4 (7.3%)	2 (13.3%)	6 (6.6%)
CONGESTIVE HEART FAILURE [9]	2 (9.5%)	3 (5.5%)	0	5 (5.5%)
DYSAESTHESIA [3]	0	3 (5.5%)	2 (13.3%)	5 (5.5%)
ELECTROCARDIOGRAM QT PROLONGED	2 (9.5%)	3 (5.5%)	0	5 (5.5%)
HYPERURICEMIA [19]	1 (4.8%)	2 (3.6%)	2 (13.3%)	5 (5.5%)
PERIPHERAL SENSORY NEUROPATHY [2]	1 (4.8%)	3 (5.5%)	1 (6.7%)	5 (5.5%)
SYNCOPE	1 (4.8%)	3 (5.5%)	1 (6.7%)	5 (5.5%)
VISION BLURRED [12]	0	4 (7.3%)	1 (6.7%)	5 (5.5%)
PLEURAL EFFUSION	0	3 (5.5%)	1 (6.7%)	4 (4.4%)

Investigator text for AEs encoded using MedDRA version 26.0.
Adult patients are defined as subjects >=18 years of age; Pediatric patients are defined as subjects <18 years of age.

CCOD: Jul 16 2023. DBL: Nov 18 2019 (GO40783), Oct 20 2020 (GO40784), Sep 7 2023 (CO40778, BO41932, GO40782)

[1] Includes the preferred terms: cognitive disorder, confusional state, disturbance in attention, disorientation, memory impairment, amnesia, mental status changes, hallucination, delirium, 'hallucination, auditory', 'hallucination, visual' & mental disorder.

[2] Includes the preferred terms: neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy

[3] Includes the preferred terms: paraesthesia, hyperaesthesia, hypoaesthesia, dysaethseia

[4] Includes the preferred terms: ataxia, balance disorder, gait disturbances

[5] Includes the preferred terms: dizziness, vertigo, dizziness postural

[6] Includes the preferred terms: face oedema, fluid retention, generalized oedema, localized oedema, oedema, oedema peripheral, peripheral swelling

[7] Includes the preferred terms: back pain, neck pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity

[8] Includes the preferred terms: bronchitis, lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection, upper respiratory tract infection

[9] Includes the preferred terms: acute right ventricular failure, cardiac failure, cardiac failure congestive, chronic right ventricular failure, ejection fraction decreased, pulmonary oedema

[10] Includes the preferred terms: neutropenia, neutrophil count decreased

[11] Includes the preferred terms: rash, rash maculopapular, rash pruritic, rash erythematous, rash papular

[12] Includes the preferred terms: diplopia, vision blurred, visual impairment

[13] Includes the preferred terms: fatigue, asthenia

[14] Includes the preferred terms: hypotension, orthostatic hypotension

[15] Includes the preferred terms: Ankle Fracture, Bursitis, Compression Fracture, Femoral Neck Fracture, Femur Fracture, Fibula Fracture, Foot Fracture, Fracture, Fractured Sacrum, Hip Fracture, Humerus Fracture, Ilium Fracture, Jaw Fracture, Limb Fracture, Lumbar Vertebral Fracture, Pathological Fracture, Rib Fracture, Spinal Compression Fracture, Spinal Fracture, Sternal Fracture, Stress Fracture, Thoracic Vertebral Fracture, Tibia Fracture, Wrist Fracture

[16] Includes the preferred terms: urinary retention, urinary incontinence, urinary hesitation, micturition disorder, micturition urgency

[17] Includes the preferred terms: hypersomnia, insomnia, sleep disorder, somnolence

[18] Includes the preferred terms: anxiety, affect lability, affective disorder, agitation, depressed mood, euphoric mood, mood altered, mood swings, irritability, depression, persistent depressive disorder, psychomotor retardation

[19] Includes the preferred terms: blood uric acid increased, hyperuricaemia

2.5.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

A total of 45 patients (49.5%) experienced at least one SAE. Fifteen patients (16.5%) experienced at least one treatment-related SAE.

The most frequent **SAEs by SOC** (≥5% of patients) were:

- Infections and infestations (19 patients [20.9%])
- Injury, poisoning, and procedural complications (16 patients [17.6%])
- General disorders and administration site conditions (10 patients [11.0%])
- Nervous system disorders (9 patients [9.9%])
- Respiratory, thoracic, and mediastinal disorders (7 patients [7.7%])
- Gastrointestinal disorders (5 patients [5.5%])

The most frequent **SAEs by PT** (≥2 patients) were:

- Pyrexia (7 patients [7.7%])
- Pneumonia, femur fracture, hydrocephalus, (5 patients each [5.5%])

- Device related infection, hypoxia, respiratory failure (3 patients each [3.3%])
- Sepsis, upper respiratory tract infection, infection, fracture, headache, gait disturbance, pain, dyspnoea, tibia fracture, vomiting (2 patients each [2.2%])

Deaths

A total of 20 deaths (22.0%) were reported (table below). All deaths were due to progressive disease. The majority of deaths occurred more than 30 days after the last dose of entrectinib.

Table 50 : Summary of fatal adverse events

Deaths, Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782, GO40783, GO40784

	NTRK-Adult (N=326)	ROS1 NSCLC-Adult (N=247)	Other-Adult (N=189)	Total-Adult (N=762)	Pediatric (N=91)	Total (N=853)
Total number of deaths	148 (45.4%)	116 (47.0%)	63 (33.3%)	327 (42.9%)	20 (22.0%)	347 (40.7%)
Primary cause by days from last study drug administration						
<=30 days						
Total number of deaths	42	44	22	108	4	112
Adverse Event	21 (50.0%)	21 (47.7%)	6 (27.3%)	48 (44.4%)	0	48 (42.9%)
Progressive Disease	21 (50.0%)	21 (47.7%)	13 (59.1%)	55 (50.9%)	4 (100%)	59 (52.7%)
Other	0	2 (4.5%)	0	2 (1.9%)	0	2 (1.8%)
Unknown	0	0	3 (13.6%)	3 (2.8%)	0	3 (2.7%)
>30 days						
Total number of deaths	106	72	41	219	16	235
Adverse Event	4 (3.8%)	1 (1.4%)	1 (2.4%)	6 (2.7%)	0	6 (2.6%)
Progressive Disease	95 (89.6%)	65 (90.3%)	29 (70.7%)	189 (86.3%)	16 (100%)	205 (87.2%)
Other	5 (4.7%)	2 (2.8%)	0	7 (3.2%)	0	7 (3.0%)
Unknown	2 (1.9%)	4 (5.6%)	11 (26.8%)	17 (7.8%)	0	17 (7.2%)

Cause of death is defined differently for each study:
ALKA-372-001 - 'Adverse Event' if death is related to adverse event, 'Progressive Disease' if death is related to cancer, 'Unknown' if selected by investigator or no cause given, 'Other' for any other reason.
RXDX-101-01 - 'Adverse Event' if death is related to adverse event, other cause of death was not collected, coded as 'Unknown'.
RXDX-101-02, RXDX-101-03, BO41932 - 'Adverse Event' if death is related to adverse event, 'Progressive Disease' if death is related to cancer, 'Other' if death is not related to cancer, 'Unknown' if death has unknown relation to cancer.
The time interval was only calculated for patients with a death event and an available last study drug administration date.
Adult patients are defined as subjects >=18 years of age; Pediatric patients are defined as subjects <18 years of age.

CCOD: Jul 16 2023, DBL: Nov 18 2019 (GO40783), Oct 20 2020 (GO40784), Sep 7 2023 (CO40778, BO41932, GO40782)

2.5.8.4. Laboratory findings

Due to differences in data collection for STARTRK-NG, TAPISTRY, and STARTRK-02, clinical laboratory assessments are presented separately for the STARTRK studies (STARTRK-NG and STARTRK-02, n=70) and TAPISTRY (n=21).

STARTK-NG and STARTRK-02

Based on laboratory data, the most frequent (≥ 2 patients) shifts observed from Grade 0-2 at baseline to Grade 3-4 post-baseline for the specific haematology parameters were:

- Neutrophils decreased (17 patients [24.3%])
- Haemoglobin decreased (5 patients [7.1%])
- Lymphocytes increased (3 patients [4.3%])
- Platelets decreased (3 patients [4.3%])
- Lymphocytes decreased (2 patients [2.9%])

TAPISTRY

Most patients (n=21) had missing shift data.

Based on laboratory data, the most frequent (≥ 2 patients) shifts observed from Grade 0-2 at baseline to Grade 3-4 post-baseline for the specific haematology parameters were:

- Neutrophils decreased (3 patients [14.3%])
- Haemoglobin decreased (2 patients [9.5%])

Chemistry

STARTRK-NG and STARTRK-02

Based on laboratory data, the most frequent (≥ 2 patients) shifts observed from Grade 0-2 at baseline to Grade 3-4 post-baseline for the specific chemistry parameters were:

- Creatinine increased (8 patients [11.4%])
- Calcium increased (7 patients [10.0%])
- Albumin decreased (7 patients [10.0%])
- Potassium decreased (5 patients [7.1%])
- Magnesium increased (4 patients [5.7%])
- Glucose increased (3 patients [4.3%])
- Phosphorus decreased (3 patients [4.3%])
- ALT increased (3 patients [4.3%])
- Sodium decreased (3 patients [4%])
- Potassium increased (3 patients [4.3%])
- AST increased (3 patients [4.3%])

TAPISTRY

Clinically relevant shifts of Grade ≥3 post baseline are provided below.

- Uric acid increased (5 patients [23.8%])

2.5.8.5. In vitro biomarker test for patient selection for safety

N/A

2.5.8.6. Safety in special populations

This extension of indication applies to paediatric patients.

2.5.8.7. Immunological events

2.5.8.8. Safety related to drug-drug interactions and other interactions

Interaction studies with other medicinal products have been performed only in adults.

2.5.8.9. Discontinuation due to adverse events

Adverse Events that led to Treatment discontinuation

Eleven patients (12.1%) experienced AEs leading to discontinuation of treatment (table below).

Table 51: Summary of Adverse Events leading to treatment discontinuation

Adverse Events, Leading to Study Treatment Discontinuation, Safety-Evaluable Patients
Protocols: GO40782, GO40783, GO40784, CO40778, BO41932

MedDRA System Organ Class MedDRA Preferred Term	NTRK-Adult (N=326)	ROS1 NSCLC-Adult (N=247)	Other-Adult (N=189)	Total-Adult (N=762)	Pediatric (N=91)	Total (N=853)
Total number of patients with at least one adverse event	48 (14.7%)	33 (13.4%)	16 (8.5%)	97 (12.7%)	11 (12.1%)	108 (12.7%)
Overall total number of events	53	40	25	118	14	132
CARDIAC DISORDERS						
Total number of patients with at least one adverse event	10 (3.1%)	9 (3.6%)	3 (1.6%)	22 (2.9%)	0	22 (2.6%)
Total number of events	10	10	4	24	0	24
CARDIAC FAILURE	0	3 (1.2%)	1 (0.5%)	4 (0.5%)	0	4 (0.5%)
CARDIAC ARREST	2 (0.6%)	1 (0.4%)	0	3 (0.4%)	0	3 (0.4%)
CARDIAC FAILURE CONGESTIVE	2 (0.6%)	1 (0.4%)	0	3 (0.4%)	0	3 (0.4%)
CARDIO-RESPIRATORY ARREST	2 (0.6%)	0	0	2 (0.3%)	0	2 (0.2%)
LEFT VENTRICULAR DYSFUNCTION	2 (0.6%)	0	0	2 (0.3%)	0	2 (0.2%)
ACUTE CORONARY SYNDROME	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
ATRIAL FIBRILLATION	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
ATRIOVENTRICULAR BLOCK	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
CARDIOGENIC SHOCK	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
EXTRASYSTOLES	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
MYOCARDITIS	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
MYOPERICARDITIS	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
PERICARDIAL EFFUSION	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
VENTRICULAR DYSFUNCTION	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
VENTRICULAR FIBRILLATION	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Total number of patients with at least one adverse event	6 (1.8%)	7 (2.8%)	3 (1.6%)	16 (2.1%)	2 (2.2%)	18 (2.1%)
Total number of events	6	8	3	17	2	19
DYSPNOEA	0	2 (0.8%)	1 (0.5%)	3 (0.4%)	1 (1.1%)	4 (0.5%)
HYPOXIA	3 (0.9%)	0	0	3 (0.4%)	0	3 (0.4%)
PULMONARY EMBOLISM	0	3 (1.2%)	0	3 (0.4%)	0	3 (0.4%)
ACUTE RESPIRATORY FAILURE	2 (0.6%)	0	0	2 (0.3%)	0	2 (0.2%)
PNEUMONITIS	1 (0.3%)	1 (0.4%)	0	2 (0.3%)	0	2 (0.2%)
PULMONARY OEDEMA	0	0	1 (0.5%)	1 (0.1%)	1 (1.1%)	2 (0.2%)
HAEMOPTYSIS	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
RESPIRATORY FAILURE	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
THROAT IRRITATION	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
NERVOUS SYSTEM DISORDERS						
Total number of patients with at least one adverse event	9 (2.8%)	3 (1.2%)	3 (1.6%)	15 (2.0%)	0	15 (1.8%)
Total number of events	9	3	4	16	0	16
CEREBROVASCULAR ACCIDENT	2 (0.6%)	1 (0.4%)	0	3 (0.4%)	0	3 (0.4%)
COGNITIVE DISORDER	1 (0.3%)	0	2 (1.1%)	3 (0.4%)	0	3 (0.4%)
CEREBRAL DISORDER	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
DYSAESTHESIA	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
ISCHAEMIC STROKE	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
LIMBIC ENCEPHALITIS	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
MEMORY IMPAIRMENT	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
MYOCLONUS	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
NEUROPATHY PERIPHERAL	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
PERIPHERAL SENSORY NEUROPATHY	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
THALAMIC INFARCTION	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
TREMOR	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)

Investigator text for AEs encoded using MedDRA version 26.0.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Adult patients are defined as subjects >=18 years of age; Pediatric patients are defined as subjects <18 years of age.

CCOD: Jul 16 2023, DBL: Nov 18 2019 (GO40783), Oct 20 2020 (GO40784), Sep 7 2023 (CO40778, BO41932, GO40782)

Program: root/clinical_studies/RO7102122/share/pool_EMA_2023/prod/program/t_ae.sas / Output: root/clinical_studies/RO7102122/share/pool_EMA_2023/prod/output/t_ae_DISTRT_SE_ACO.out
05OCT2023 15:45 Page 1 of 4

The most frequent AEs by SOC (≥2 patients) that led to discontinuation of treatment were injury, poisoning, and procedural complications (6 patients [6.6%]) and Respiratory, thoracic, and mediastinal disorders (2 patients [2.2%]).

The most frequent AEs by PT (≥2 patients) were tibia fracture (3 patients) and femur fracture(2 patients).

Adverse Events that led to Dose Reduction

Twenty-two patients (24.2%) experienced AEs leading to dose reduction of entrectinib (table below).

The most frequent AEs by SOC (≥2 patients) that led to dose reduction were:

- Investigations (14 patients [15.4%])
- Injury, poisoning, and procedural complications (2 patients [2.2%])
- Nervous system disorders (2 patients [2.2%])

The most frequent AEs by PT (≥2 patients) that led to dose reduction were:

- Weight increased (9 patients [9.9%])
- Blood creatinine increased (2 patients [2.2%])

Table 52 : Summary of Adverse Events leading to Dose Reduction

Adverse Events, Leading to Dose Reduction, Safety-Evaluable Patients
Protocols: GO40782, GO40783, GO40784, CO40778, BO41932

MedDRA System Organ Class MedDRA Preferred Term	NTRK-Adult (N=326)	ROS1 NSCLC-Adult (N=247)	Other-Adult (N=189)	Total-Adult (N=762)	Pediatric (N=91)	Total (N=853)
Total number of patients with at least one adverse event	87 (26.7%)	86 (34.8%)	30 (15.9%)	203 (26.6%)	22 (24.2%)	225 (26.4%)
Overall total number of events	136	154	43	333	29	362
NERVOUS SYSTEM DISORDERS						
Total number of patients with at least one adverse event	32 (9.8%)	33 (13.4%)	10 (5.3%)	75 (9.8%)	2 (2.2%)	77 (9.0%)
Total number of events	39	50	13	102	2	104
DIZZINESS	14 (4.3%)	16 (6.5%)	6 (3.2%)	36 (4.7%)	0	36 (4.2%)
COGNITIVE DISORDER	5 (1.5%)	4 (1.6%)	0	9 (1.2%)	0	9 (1.1%)
ATAXIA	3 (0.9%)	3 (1.2%)	1 (0.5%)	7 (0.9%)	0	7 (0.8%)
PARAESTHESIA	1 (0.3%)	5 (2.0%)	0	6 (0.8%)	0	6 (0.7%)
PERIPHERAL SENSORY NEUROPATHY	1 (0.3%)	3 (1.2%)	2 (1.1%)	6 (0.8%)	0	6 (0.7%)
DYSGEUSIA	2 (0.6%)	1 (0.4%)	0	3 (0.4%)	1 (1.1%)	4 (0.5%)
DYSARTHRIA	1 (0.3%)	2 (0.8%)	0	3 (0.4%)	0	3 (0.4%)
NEUROPATHY PERIPHERAL	2 (0.6%)	1 (0.4%)	0	3 (0.4%)	0	3 (0.4%)
SOMNOLENCE	1 (0.3%)	2 (0.8%)	0	3 (0.4%)	0	3 (0.4%)
BALANCE DISORDER	0	1 (0.4%)	1 (0.5%)	2 (0.3%)	0	2 (0.2%)
HYPERAESTHESIA	2 (0.6%)	0	0	2 (0.3%)	0	2 (0.2%)
MEMORY IMPAIRMENT	1 (0.3%)	1 (0.4%)	0	2 (0.3%)	0	2 (0.2%)
APHASIA	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
COORDINATION ABNORMAL	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
DEPRESSED LEVEL OF CONSCIOUSNESS	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
DISTURBANCE IN ATTENTION	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
DYSKINESIA	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
HEMIPARESIS	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
HYPERSOMNIA	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
LUMBOSACRAL RADICULOPATHY	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
MIGRAINE	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
POLYNEUROPATHY	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
SYNCOPE	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
TREMOR	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
HEADACHE	0	0	0	0	1 (1.1%)	1 (0.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Total number of patients with at least one adverse event	22 (6.7%)	19 (7.7%)	8 (4.2%)	49 (6.4%)	1 (1.1%)	50 (5.9%)
Total number of events	25	23	8	56	1	57
FATIGUE	8 (2.5%)	5 (2.0%)	1 (0.5%)	14 (1.8%)	1 (1.1%)	15 (1.8%)
ASTHENIA	6 (1.8%)	3 (1.2%)	2 (1.1%)	11 (1.4%)	0	11 (1.3%)
GAIT DISTURBANCE	3 (0.9%)	5 (2.0%)	1 (0.5%)	9 (1.2%)	0	9 (1.1%)
OEDEMA PERIPHERAL	1 (0.3%)	5 (2.0%)	1 (0.5%)	7 (0.9%)	0	7 (0.8%)
GENERALISED OEDEMA	2 (0.6%)	0	3 (1.6%)	5 (0.7%)	0	5 (0.6%)
OEDEMA	2 (0.6%)	3 (1.2%)	0	5 (0.7%)	0	5 (0.6%)
CHILLS	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
LOCALISED OEDEMA	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
PERIPHERAL SWELLING	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)

Investigator text for AEs encoded using MedDRA version 26.0.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Adult patients are defined as subjects >=18 years of age; Pediatric patients are defined as subjects <18 years of age.

CCOD: Jul 16 2023, DBL: Nov 18 2019 (GO40783), Oct 20 2020 (GO40784), Sep 7 2023 (CO40778, BO41932, GO40782)

Program: root/clinical_studies/RO7102122/share/pool_EMA_2023/prod/program/t_ae.sas / Output: root/clinical_studies/RO7102122/share/pool_EMA_2023/prod/output/t_ae_DOSRED_SE_ACO.out
05OCT2023 15:47 Page 1 of 5

Adverse Events that led to Dose Interruption

A total of 38 patients (41.8%) experienced AEs leading to dose interruption of entrectinib (table below).

The most frequent AEs by SOC (≥5% of patients) that led to dose interruption were as follows:

- Infections and infestations (21 patients [23.1%])
- Investigations (14 patients [15.4%])
- General disorders and administration site conditions (11 patients [12.1%])
- Gastrointestinal disorders (10 patients [11.0%])

- Blood and lymphatic system disorders (6 patients [6.6%])
- Respiratory, thoracic, and mediastinal disorders (5 patients [5.5%])

The most frequent AEs by PT (≥ 5% patients) that led to dose interruption were as follows:

- Pyrexia (9 patients [9.9%])
- Neutrophil count decreased (8 patients [8.8%])
- Vomiting (6 patients [6.6%])
- Covid-19 (5 patients [5.5%])

Table 53 : Summary of Adverse Events leading to Dose Interruption

Adverse Events, Leading to Dose Interruption, Safety-Evaluable Patients
Protocols: G040782, G040783, G040784, C040778, BO41932

MedDRA System Organ Class MedDRA Preferred Term	NTRK-Adult (N=326)	ROS1 NSCLC-Adult (N=247)	Other-Adult (N=189)	Total-Adult (N=762)	Pediatric (N=91)	Total (N=853)
Total number of patients with at least one adverse event	185 (56.7%)	127 (51.4%)	86 (45.5%)	398 (52.2%)	38 (41.8%)	436 (51.1%)
Overall total number of events	542	320	258	1120	206	1326
INFECTIONS AND INFESTATIONS						
Total number of patients with at least one adverse event	56 (17.2%)	30 (12.1%)	15 (7.9%)	101 (13.3%)	21 (23.1%)	122 (14.3%)
Total number of events	77	36	21	134	48	182
PNEUMONIA	10 (3.1%)	6 (2.4%)	4 (2.1%)	20 (2.6%)	4 (4.4%)	24 (2.8%)
COVID-19	12 (3.7%)	3 (1.2%)	1 (0.5%)	16 (2.1%)	5 (5.5%)	21 (2.5%)
URINARY TRACT INFECTION	6 (1.8%)	6 (2.4%)	2 (1.1%)	14 (1.8%)	1 (1.1%)	15 (1.8%)
UPPER RESPIRATORY TRACT INFECTION	3 (0.9%)	3 (1.2%)	1 (0.5%)	7 (0.9%)	2 (2.2%)	9 (1.1%)
SEPSIS	4 (1.2%)	1 (0.4%)	1 (0.5%)	6 (0.8%)	2 (2.2%)	8 (0.9%)
GASTROENTERITIS	4 (1.2%)	1 (0.4%)	1 (0.5%)	6 (0.8%)	0	6 (0.7%)
BRONCHITIS	3 (0.9%)	2 (0.8%)	0	5 (0.7%)	1 (1.1%)	6 (0.7%)
PNEUMONIA ASPIRATION	4 (1.2%)	0	0	4 (0.5%)	0	4 (0.5%)
DEVICE RELATED INFECTION	1 (0.3%)	0	0	1 (0.1%)	3 (3.3%)	4 (0.5%)
LOWER RESPIRATORY TRACT INFECTION	2 (0.6%)	0	0	2 (0.3%)	1 (1.1%)	3 (0.4%)
INFECTION	0	1 (0.4%)	0	1 (0.1%)	2 (2.2%)	3 (0.4%)
ARTHRITIS BACTERIAL	1 (0.3%)	1 (0.4%)	0	2 (0.3%)	0	2 (0.2%)
INFLUENZA	2 (0.6%)	0	0	2 (0.3%)	0	2 (0.2%)
LOCALISED INFECTION	0	2 (0.8%)	0	2 (0.3%)	0	2 (0.2%)
PYELONEPHRITIS	1 (0.3%)	1 (0.4%)	0	2 (0.3%)	0	2 (0.2%)
RESPIRATORY TRACT INFECTION	0	1 (0.4%)	1 (0.5%)	2 (0.3%)	0	2 (0.2%)
STAPHYLOCOCCAL BACTERAEMIA	1 (0.3%)	1 (0.4%)	0	2 (0.3%)	0	2 (0.2%)
ABDOMINAL ABSCESS	1 (0.3%)	0	0	1 (0.1%)	1 (1.1%)	2 (0.2%)
PHARYNGITIS	1 (0.3%)	0	0	1 (0.1%)	1 (1.1%)	2 (0.2%)
NASOPHARYNGITIS	0	0	0	0	2 (2.2%)	2 (0.2%)
VARICELLA	0	0	0	0	2 (2.2%)	2 (0.2%)
VIRAL INFECTION	0	0	0	0	2 (2.2%)	2 (0.2%)
ABDOMINAL INFECTION	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
CELLULITIS	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
ENDOCARDITIS	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
ERYSIPELAS	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
EXTRADURAL ABSCESS	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
GASTROENTERITIS ROTAVIRUS	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
GASTROENTERITIS VIRAL	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
GASTROINTESTINAL INFECTION	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
HERPES ZOSTER	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
INTERVERTEBRAL DISCITIS	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
KLEBSIELLA SEPSIS	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
MENINGITIS VIRAL	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
OESOPHAGEAL CANDIDIASIS	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
PERINEPHRITIS	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
PNEUMONIA BACTERIAL	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
PNEUMONIA VIRAL	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
PULPITIS DENTAL	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
PYELONEPHRITIS ACUTE	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
RASH PUSTULAR	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
SCROTAL ABSCESS	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
SEPTIC SHOCK	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
SHUNT INFECTION	0	1 (0.4%)	0	1 (0.1%)	0	1 (0.1%)
SKIN INFECTION	0	0	1 (0.5%)	1 (0.1%)	0	1 (0.1%)
STAPHYLOCOCCAL SEPSIS	1 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)

Investigator text for AEs encoded using MedDRA version 26.0. ** uncoded preferred term (if present) replaced by investigator text
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Adult patients are defined as subjects >=18 years of age; Pediatric patients are defined as subjects <18 years of age.

CCOD: Jul 16 2023, DBL: Nov 18 2019 (GO40783), Oct 20 2020 (GO40784), Sep 7 2023 (CO40778, BO41932, GO40782)

2.5.8.10. Post marketing experience

Rozlytrek received a conditional marketing authorisation in the EU on 31 July 2020, and the International Birth Date (IBD) is set to 18 June 2019.

The estimated cumulative exposure from post-marketing sources, up until the DLP is 2,328 patients worldwide. The majority of these patients were in the US (n=1,380), followed by Japan (n=487). There were 259 patients in the EEA and 202 in the rest of the world.

Data from the fifth EU PSUR for Rozlytrek (entrectinib) covering the period 18 June 2022 to 17 December 2022 have been recently assessed.

Long-term follow-up studies

Study CO40778 (STARTRK-NG) involving entrectinib stipulates a long-term follow-up interval of at least 5 years after first dose or until study drug discontinuation, whichever occurs first. The purpose of this follow-up interval is to monitor the long-term effects of entrectinib in the growth and development of paediatric patients. The follow-up will include monitoring of growth, puberty, and neurocognitive development as well as specific measures for bone health.

Study BO41932 (TAPISTRY) involving entrectinib stipulates a long-term survival follow-up, where in, patients at the first two scheduled visits after discontinuation of the treatment (at 3 months and 6 months) or study withdrawal, whichever occurs first are followed to collect information related to patient-reported outcomes, specific growth and development assessments (<18 years), neurocognitive assessments (<18 years), and new anti-cancer therapy.

Safety in long-term use is considered missing information with entrectinib, as there are comparatively limited data on the safety of entrectinib in patients treated beyond ≥12 months of treatment. This risk continues to be further assessed as part of Study GO40782 [STARTRK-2], CO40778 [STARTRK-NG] and BO41932 (TAPISTRY).

2.5.9. Discussion on clinical safety

In support of the safety profile of entrectinib the MAH has submitted safety data coming from three ongoing studies: STARTRK-NG (n = 68), TAPISTRY (n = 21), and STARTRK-02 (n = 2) which were pooled and analysed collectively as integrated safety population (n = 91) with a clinical cutoff date (CCOD) of 16 July 2023. Specifically, with reference to the age range (> 6 months of age to 12 years) of this extension of indication data are available from 53 patients (of whom 14 patients 0 to <2 years of age, 49 2 to <12 years, and 13 patients are adolescents which is an age range already covered by the initial MA.

Results of the updated analysis (16 July 2023 CCOD) based on 91 entrectinib-treated paediatric patients in the integrated safety population, including 50 patients with NTRK gene fusions and 23 patients with ROS1 gene fusions have been provided during the procedure.

The integrated safety population is characterised by a significant heterogeneity including subjects regardless important variables, such as drug formulation, dosing regimen, duration of treatment and tumour type, potentially impacting the safety profile of the drug. Moreover, the agnostic indication and the uncontrolled design of all the studies included in the analysis is a further limitation to clearly characterize entrectinib-related adverse events (AEs) and potential differences related to underlying malignancies.

Overall, the size of the entrectinib safety database in the claimed indication is of limited size, yet considered adequate due to the rarity of the genetic/molecular subtypes of tumours.

The median total duration of treatment was 11.1 months (range 0.1-56.0 months).

Long-term safety is considered a missing information in the entrectinib RMP, as there are comparatively limited data on the safety of entrectinib in patients treated beyond ≥12 months of treatment. The last PSUR did not identify new safety information.

Almost all (98.9%) of patients experienced at least one AE. 89.0% of patients experienced at least one AE related to the study drug per the Investigator and 49.5% of patients experienced SAEs (16.5% experienced treatment related SAEs. In the integrated safety population 12.1% (11 patients) of patients experienced an AEs leading to treatment discontinuation with fractures as the most frequent reported AE. Overall, the proportion of patients with AEs leading to treatment discontinuation is relatively low. Dose Interruptions and reduction were observed in 41.8% and 24.2% of patients, respectively, with no specific pattern of AEs identifiable. Similar proportions in dose interruption/reduction have been observed in adults/adolescents studies.

In total 20 deaths were reported, all classified as due to progression of disease. In the majority of cases time of occurrence (more than 30 days after last dose of entrectinib) is not suggesting a causal relationship with the drug.

Adverse drug reactions (ADRs) were defined at the time of the initial MAA. The same ADRs apply for the paediatric age. Moreover, in order to disentangle the tolerability of entrectinib across paediatric ages included in the studies, AEs (reflecting all ADRs included in the 4.8 of the SmPC) by severity grades (including SAEs and deaths) were provided, stratifying patients according to age categories 0-6 months, 6 months- 2 years, 2-6 years, 6-11 years and adolescents. Safety data reported by age ranges showed a higher frequency of SAEs in the lower age ranges (0-6 months and 6 months-2 years, 75% and 71.4%, respectively) as compared to older age ranges (>2 years) with infections and infestations being the most common reported AEs; none of these events led to drug discontinuation. Infections were mainly of the urinary and respiratory tract and as AEs could be clinically expected in paediatric patients below 3 years of age more than in older ages and in the context of an anticancer treatment.

In the age ranges 2-6 years and 6-12 years, SAE frequency was 57.1% and 41.9%, respectively with injuries (fractures) being the most common. Adverse events leading to drug discontinuation were reported in 21% of patients in the age range 2-12 years. . A specific pattern in distribution of the most relevant ADRs is not noted across age ranges with the exception of fractures (highest frequency in the 6-12 years range) and infections (urinary and lung) in the lowest age ranges (0-6 months, 6 months-2 years)Although numbers are limited in the different age groups and hence sound conclusions could not be made, the provided data offers some granularity of entrectinib tolerability across age ranges but do not highlight a specific trend of ADRs occurrence (including severity grades) across ages with the exception of fractures in particular in the age range 6-12 years and infections (urinary and lung) in the lowest age ranges (0-6 months, 6 months-2 years) which could be expected in paediatric patients below 3 years of age with immature immune system more than in older ages and in the context of an anticancer treatment.

AESI

Bone fractures:

Fractures are confirmed as the most frequently occurring (>5%) ADR: when considered as any grade, a total of 27 out of 91 patients (29.7%) experienced a bone fracture event with the highest frequency in the age range 6-12 years (42.9%). Fractures were also the most frequently occurring (>5%) serious ADR in all age groups (13.2%). Grade 3 events occurred most frequently in the age group >6 years to < 12 years (7/31 patients [22.6%]). There were no Grade 4 events.

Fractures are classified as ADR in the 4.8 section of the SmPC with common frequency in the infants and toddlers and as very common in children and adolescents. Hence, occurrence is quite higher in the paediatric age as compared with adults/adolescent with a not negligible difference of roughly 15%. In the majority of

cases fractures were resolved. Four patients had unresolved fracture events and 6 patients had discontinued drug due to fractures. The section 4.2 of the SmPC does not include modification of the posology. Data available on fracture outcome (including time to recovery) in patients who discontinued/reduced the posology of entrectinib as compared to those patients who did not, are not conclusive however not suggestive of an impact of dose modifications in fracture resolution. Almost all fracture events were localized in the lower body, some but not all occurred in the setting of fall/trauma. In the STARTRK-NG study only a minority (12/27) of subjects experiencing fractures used corticosteroids. Other concurrent risk factors for development of fractures (e.g. radiation, stem cell transplantation, reduced vitamin D levels) were also reported but the potential role of risk factors is still unclear. Though, a direct role of entrectinib on bone fracture risk cannot be excluded due to the impact on physiological bone remodelling processes.

Fractures, particularly in the paediatric age, can be debilitating , requiring a period of recovery, could expose subjects to further risks such as surgery and/or immobilization and overall further complicate a clinical condition which is per se complex.

A stepwise machine-learning based methodology was provided in order to investigate the pathophysiological molecular mechanisms related to increased bone fracture risk, identification of measurable biomarkers and eventually selection of possible treatments. The methodology is of interest and might potentially support the achievement of key findings connected to the molecular mechanisms behind increased bone fracture risk linked to entrectinib treatment. However, the submitted information is still insufficient for a comprehensive understanding and evaluation of the risk. Importantly, the proposed models still miss validation in terms of credibility assessment therefore the context of use should be considered at present as only exploratory and preliminary but not for clinical use.

Fractures are classified as important identified risk in the RMP. Patients with signs or symptoms of fractures (e.g., pain, abnormal gait, changes in mobility, deformity) should be evaluated promptly, warning in section 4.4 the SmPC was deemed sufficient to address this risk. An integrated safety analysis report to assess the risk of fracture based on STARTRK-2, STARTRK-NG, and TAPISTRY studies is aimed to characterize the risk of fractures in paediatric patients (collection of blood markers of bone metabolism and reabsorption, and regularly scheduled DXA scans and hand and knee x-rays). The final integrated safety analysis report will better characterize the risk and is reflected as an Additional Pharmacovigilance Activities (category 3) in the RMP.

Cardiac toxicity

Congestive heart failure: The mechanism underlying CHF in entrectinib-treated patients is currently unknown. In the Integrated safety data set, a total of 11 events were recorded with one patient having Grade > 2 congestive heart failure with Grade 4 pulmonary oedema assessed related to entrectinib and resolved after drug withdrawal. In the 4.8 section of the SmPC congestive heart failure is an ADR reported with frequency common. Occurrence could be observed in subjects with or without classical risk factors among them commonly used chemotherapy agents with known cardiac toxicity should be considered. Sections 4.2 and 4.4 of the SmPC provide monitoring, dose modification recommendations and management guidelines to reduce the potential risk for CHF which also apply to paediatric subjects. Cardiac heart failure is classified as an important identified risk. he final integrated analysis report for cardiac risks (cat 3 study in the RMP) was submitted in procedure EMEA/H/C/004936/II/0012. The SmPC section 4.4 has been updated accordingly.

QT prolongation: A defined mechanism to explain the QT-prolonging effects of entrectinib is unknown; a plausible hypothesis is that the three-dimensional structural configurations of TKIs uniquely interact with hERG potassium current resulting in QT prolongation. 5 (5.5%) patients experienced QT prolongation events

(any grade); 3 patients (3.3%) had Grade 1 events and two patients (2.2%) had Grade 2 events. No patients reported an event of QT interval prolongation Grade > 2. None of the QT prolongation events in this population was reported as serious or unresolved. QT prolongation is classified as an identified risk in the RMP. A summary of QT prolongation events (any grade not only > grade 2) registered in the integrated safety analysis also by stratifying subjects according to the age ranges (0-6 months, 6 months- 2 years, 2-6 years, 6-12 years, by grade and outcome) was provided. A specific trend could not be identified, also in specific age ranges; overall events were non serious and resolved.

The section 4.2 of the SmPC includes dose modifications for the ADR QT interval prolongation and section 4.4 recommends an "Assessment of ECG and electrolytes at baseline and after 1 month of treatment with Rozlytrek". In addition, "Periodic monitoring of ECGs and electrolytes as clinically indicated throughout Rozlytrek treatment, are also recommended", the same indications in place for adults and adolescents apply for the paediatric age. No additional RMMs are in place. However, the risk continues to be further assessed as part of PASS GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY] (see RMP).

Cardiac arrhythmia is an event under close monitoring and during the last PSUR evaluation for some cases a causal association cannot be excluded. Clarification on registered cases of Cardiac Arrhythmia was provided by the MAH including a discussion about causality, all the events were non-serious, except one event of syncope (not associated with cardiac arrhythmia). The majority (81.6%) of the events had resolved; only in few patients a dose modification was applied. The median time of appearance was 79.5 days. Most patients had received prior anticancer therapies.

A cumulative search in entrectinib dataset identify 117 cases no specific type of arrhythmia was found. The available evidence is insufficient to establish the role of entrectinib in increasing the risk of cardiac arrhythmias. These events will continue to be monitored through routine pharmacovigilance activities (see RMP).

Neurologic toxicity: In light of entrectinib mechanism of action and prevalent expression of TRK receptors in nervous tissues, neurologic toxicity, involving both central and peripheral nervous system, was observed. Heterogeneous AEs are reported in the SmPC; assessment of neurologic toxicity is further complicated by the underlying tumour (CNS primary or CNS metastasis) as well as previous treatments (chemotherapy and/or radiotherapy) evoking neurological toxicities. To have a comprehensive view of neurologic ADRs in the paediatric integrated safety data set a table reporting neurologic ADRs (including type of tumour, AE severity, and outcome, risk factors) the MAH was asked to provide such data. Half of paediatric patients (49.5%) experienced neurologic AEs (Nervous System Disorders system organ class [SOC]) of which only 1 (1.1%) patient experienced Grade 4 event and 8 (8.8%) patients experienced Grade 3 events. Less than 20% had events not resolved with higher frequency in those patients with baseline CNS disease.

The presence of CNS disease at baseline (including tumour, metastasis) was not related to the occurrence of CNS ADRs, equally distributed between patients with and without CNS disease; indeed, the presence of baseline disease negatively impacts the severity and outcome of experienced CNS ADRs. Regarding seizures three events were registered without demonstration of causality.

Cognitive disorders including confusion, mental status changes, memory impairment, and hallucinations, have been reported and is classified as an ADR. For the integrated safety data set the MAH has not provided a clear reporting of cognitive disturbances (any grade) but only Grade > 2. Considering single studies, from STARTR-NG and TAPISTRY studies, a total of 9 cognitive disorders events (1 grade >2) and no cases in the study STARTRK-2 have been reported. Information on cognitive disorders (any grade) stratified by age ranges, severity grade and outcome in the integrated safety data set has been provided: 9 patients

experienced 12 cognitive disorder events (4 codified as related) these were mild and moderate in severity. The SmPC in section 4.2 provide recommendation of dose modifications, however no conclusion on the impact of dose reduction on outcome could be made since dose was modified (interrupted) only in one patient due to underlying disease progression.

Severe Neurological Reactions are classified as an important potential risk. Routine RMMs are in place (4.2 dose reduction, 4.4. cognitive disorders). Risk continues to be further assessed as part of studies GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY] (see RMP).

Neuro-developmental impairment in paediatric patients is classified as an important potential risk in the RMP. The SmPC provides recommendations on risk management approach (4.2, 4.2, 5.3). The potential impact of neuro-developmental impairment on children such as memory impairment seems, at present, not to potentially makes risks to negatively outweigh the benefits in patients with locally advanced disease or non-pretreated or with long life expectancy. Mature data on efficacy and safety from the post market will help to better address the issue. No additional risk-minimization measures are foreseen but additional pharmacovigilance activities aimed to assess the risk through the studies STARTRK-NG and TAPISTRY are in place (see RMP).

Among other selected AEs, changes in weight are reported in 38.5% of subjects likely as consequence of TRK inhibition by entrectinib.

Laboratory findings: for haematology parameters the most frequent (≥ 5 patients) shifts from Grade 0-2 at baseline to Grade 3-4 post-baseline were for neutrophils decreased and haemoglobin decreased (20/91 and 7/91, respectively). For chemistry the most frequent (≥ 5 patients) shifts from Grade 0-2 at baseline to Grade 3-4 post-baseline were observed for albumin and calcium increased (7 patients each), potassium decreased, and uric acid increased (5 patients each). Creatinine increased (it is an ADR) occurred in 8 patients. Creatinine increased is an ADR, in the last PSUR 38 events (38 cases) of acute renal failure of these, 28/38 concerned the PT blood creatinine increased, have been identified. No acute renal failure event was reported.

Supportive safety data and post-marketing experience

Rozlytrek received a conditional marketing authorisation in the EU on 31 July 2020, and the International Birth Date (IBD) is set to 18 June 2019. The estimated cumulative exposure from post-marketing sources, up until the DLP is 2,328 patients worldwide. The majority of these patients were in the US (n=1,380), followed by Japan (n=487). There were 259 patients in the EEA and 202 in the rest of the world. Data from the fifth EU PSUR for Rozlytrek (entrectinib) covering the period 18 June 2022 to 17 December 2022 have been recently assessed. No new safety information was identified from long-term follow-up during the reporting period.

Additional safety data needed in the context of a conditional MA:

The current ongoing SOBs will be used to provide comprehensive data also for the new NTRK paediatric indication (due date 31 March 2027). The increased sample size would also allow to collect further safety data in the paediatric population (approximately 115 entrectinib-treated patients aged ≤ 18 years old are expected in the overall safety database). The expected increased sample size of paediatric patients, together with the data in adult awaited to further confirm the NTRK histology independent efficacy of entrectinib, are likely to provide comprehensive data.

2.5.10. Conclusions on the clinical safety

Overall, the entrectinib safety database in the claimed indication is of limited size, yet considered adequate due to the rarity of the genetic/molecular subtypes of tumours.

The integrated safety population is characterised by a significant heterogeneity including subjects regardless of the formulation, dosing regimen, and duration of treatment and tumour type and does not provide data according to these important variables potentially impacting the safety profile of the drug. Moreover, the agnostic indication and the uncontrolled design of all the studies included in the analysis is a further limitation to clearly characterize entrectinib-related adverse events (AEs) and potential differences related to underlying malignancies.

The safety profile seems consistent with the known safety profile of entrectinib. Although numbers are limited in the different age groups and hence sound conclusions could not be made, the reported data do not highlight a specific trend of ADRs occurrence (including severity grades) or tolerability issues across ages with the exception of fractures any grade in 31.6% of patients aged less than 12 years and infections (urinary and lung) in the lowest age ranges (0-6 months, 6 months-2 years).

Long-term safety is still considered a missing information (see RMP), yet the last PSUR did not identified new safety findings.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- 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. The results should be submitted by 31 March 2027.
- In order to further investigate the impact of the presence/absence of other molecular alteration on the efficacy of entrectinib, the MAH should submit the results from tumour genomic profiling by plasma and/or tissue when possible at baseline and progression together with clinical outcomes association per tumour histology for the patients from the updated pooled analysis. The results should be submitted by 31 March 2027.

2.6. Risk Management Plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.2 with the following content:

2.6.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 54 : 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

2.6.2. Pharmacovigilance plan

Table 55 : Ongoing and planned additional pharmacovigilance activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Date(s)**
Category 3 Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA) – i.e., studies that investigate a safety concern or evaluate the effectiveness of risk-minimization activities				
Integrated safety analysis report to assess risk of fracture based on GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY] studies	Report to characterize the risk of fractures in paediatric patients where the following bone biomarkers will be assessed: Serial assessments of BMD with DXA; bone biomarkers in blood and assessment of potential impairment of bone growth with serial hand/wrist and knee X-rays. Clinical summary of fracture events.	Risk of fractures	Final integrated analysis report for bone biomarkers	31 March 2025
			Interim report will include clinical summary of fracture events	With annual re-assessment
	Report to characterize the risk of fractures in adult patients where the following bone biomarkers will be assessed: Serial assessments of bone mineral density (BMD) with dual X-ray absorptiometry (DXA) and bone biomarkers in blood. Clinical summary of fracture events.	Risk of fractures	Final integrated analysis report for bone biomarkers	31 March 2025
			Interim report will include clinical summary of fracture events	With annual re-assessment

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

2.6.3. Risk minimisation measures

Table 56 Summary table of pharmacovigilance activities and risk-minimization activities by safety concern

Safety concern	Risk Minimization Measures	Pharmacovigilance Activities
Fractures	**Routine risk-minimization measures:** SmPC Section 4.4 (Fractures) and Section 4.8 (undesirable effects) of the SmPC provide recommendations on risk management approach **Additional risk-minimization 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 integrated safety analysis reports based on PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].
Congestive Heart Failure	**Routine risk-minimization 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-minimization 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-minimization 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-minimization 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-minimization measures:** SmPC Sections 4.2 (Dose modifications), Section 4.4 (Cognitive disorders) and Section 5.3 – (Juvenile rat toxicology study provides available information in animal studies) provide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Risk continues to be further assessed as part of PAES CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].

Safety concern	Risk Minimization Measures	Pharmacovigilance Activities
	recommendations on risk management approach if neurocognitive changes development. **Additional risk-minimization measures:** None	
Severe Neurologic Reactions	**Routine risk-minimization 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-minimization 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-minimization measures:** None **Additional risk-minimization 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].

2.6.4. Conclusion

The CHMP considered that the risk management plan version 5.2 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

Preparation and use of the nasogastric or oral suspension (in water or milk):
The preparation of oral suspension using Rozlytrek capsules is not limited to the HCPs in an hospital setting, but it has to be prepared daily by parents or caregivers. The preparation of the oral suspension is based on several steps. The intervention of the HCP consists in providing information on how many capsules to be used, the exact volume of water or milk in which disperse the content of opened capsule(s) and the exact volume of suspension to withdrawn to administer the prescribed dose. The rest of preparation/administration is up to parents/caregivers.
Some important aspects are to be noted: patients/caregiver have to measure two volumes (ml), one is the volume of milk or water to add to the capsule(s) content to make the suspension and the other one is the volume of the suspension to withdrawn to reach the prescribed dose; just a fraction of the prepared suspension is to be administered (except some cases in which the entire content of the capsule should be administered).

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet of capsule and film-coated granules submitted by the MAH show that the package leaflets meet the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

Instruction for use are included at the end of both PL.
Despite the complexity in preparing the suspension with capsule(s), just few questions of the initially submitted full user test pertained the IFU of the capsule. Several amendments have been implemented to ensure that the IFU is clear and comprehensive particularly regarding the preparation of oral suspension. Although, these amendments could adequately address the risk, the MAH is requested to perform a focused UT on the finalized IFU after 6 months from the opinion to confirm its understandability by patients/caregivers (**REC**).

2.8.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the MAH and has been found acceptable by the QRD Group for the following reasons:

As part of the application for the new pharmaceutical form and strength (50 mg coated granules), the MAH has requested an exemption from the obligation that certain particulars appear on the sachets, i.e., the pharmaceutical form and the method and route of administration. The company claimed that the omission of this information would enable a simplified label on the sachet that could be used in all Member States to address patient demands in a sustainable manner within a reasonable timeframe.

The main grounds to justify the request were the very low number of paediatric patients expected in the EU, the difficulties in their manufacturing process to produce country-specific sachets, the distribution and cost implications, and the fact that the readability of the multilingual sachets would be compromised by having to use a small font size (6pt max).

Outcome: The QRD Group expressed a preference for having the information in English only rather than omitting certain elements on the sachet. Therefore, the labelling exemption was considered acceptable, if the request to have an EN only sachet can be fulfilled by the company.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials

will only be translated in the language(s) as agreed by the QRD Group.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

With this procedure the indication of Rozlytrek is updated to the following (addition in **bold**, deletion ~~strikethrough~~):

Neurotrophic tyrosine receptor kinase (NTRK) gene fusion

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients ***older than 1 month*** *~~12 years of age and older~~ with solid tumours* ***that have a*** *~~expressing 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 (see sections 4.4 and 5.1).*

3.1.2. Available therapies and unmet medical need

In the "last-line" setting in locally advanced, metastatic or where surgical resection is likely to result in severe morbidity and with no satisfactory treatment options. Entrectinib keeps already the site and histology independent NTRK indication covering adult and adolescent >12 years of age (extrapolation from adult to adolescent was accepted at the initial CMA, further no age-specific drug formulation was yet available). The same paediatric indication sought by entrectinib (from birth) is covered by larotrectinib (Vitrakvi), which is currently approved in EU under CMA. In the paediatric sub-population (n=70), Vitrakvi showed an ORR of 87%. An oral solution of Vitrakvi is available for patients who cannot swallow the capsules[41].

3.1.3. Main clinical studies

The MAH presented pooled efficacy and safety analyses to support the NTRK and ROS1 sought indications of entrectinib, including selected paediatric patients enrolled and treated in STARTRK-NG (main study), TAPISTRY and STARTRK-02 (supportive studies). STARTRK-NG, the paediatric study in the entrectinib programme, is a phase I/II single arm study including a paediatric dose escalation and dose expansion cohorts.

[41] Summary of Product Characteristics – Vitrakvi https://www.ema.europa.eu/en/documents/product-information/vitrakvi-epar-product-information_en.pdf accessed July 2023

To support **efficacy**, a pooled analysis was provided, and which has been updated during the procedure (CCOD 16 July 2023 for NTRK):

- **NTRK Integrated Efficacy Population**: **n = 44** patients (range 1.3 months - 15 years).

Within the pooled dataset, patients met the following criteria:

- Age <18 years
- Had tumours that harbour a NTRK gene fusion
- No prior treatment with NTRK inhibitors
- Measurable or evaluable disease at baseline
- Received at least 1 dose of entrectinib
- Had at least 6 months of follow-up

To support safety, an Integrated Safety population including **n=91** patients (range 1.3 months – 17 years) from the three ongoing studies STARTRK-NG (n = 68), TAPISTRY (n = 21), and STARTRK-02 (n = 2) were pooled and analysed collectively with a clinical cutoff date (CCOD) of 16 July 2023.

3.2. Favourable effects

- In the updated NTRK integrated efficacy dataset (n=44), entrectinib showed a confirmed ORR by BICR of 72.7% (32 confirmed responses) (95%CI 57.21, 85.04), with high rate of CR (45.5%). Results were consistent with initially submitted dataset (n=33, ORR 69.7%).
- Responses appeared durable, with median DOR NE (95%CI 25.4, NE). 90% of patients have responses longer than 6 months, and 60% longer than 12 months.
- By tumour types: responses were observed in patients with primary CNS (10/20, ORR 50%, 95%CI 27.2, 72.8), although higher ORR was recorded in extracranial solid tumours (10/11 infantile fibrosarcoma, ORR 90.9%; spindle cell 8/8, ORR 100%).
- By ages: responses were seen across subgroups analysed: <2 years ORR 64.3% (9/14); 2-12 years ORR 79.2% (19/24); 12-18 years ORR 66.7% (4/6).
- In the age range **from 1 month to ≤6 months**, PBPK models have limited simulation properties and are therefore inadequate to support dosing recommendations in younger children. The amount of observed PK data is very limited and biased by several uncertainties providing only minor supportive evidence for dose recommendation. However, the positive benefit/risk balance in this population is derived mostly from clinical evidence: the antitumor activity shown by entrectinib in the age range 0-6 months (8/10 responders) supports including younger children (<6 months) in the entrectinib indication.
- **In the age range > 6 months – 6 years**, the review of the additional provided pcVPCs, stratified by age, body weight and formulation, identified biased simulation properties of the popPK model for patients younger than 6 years. Although the observed PK data are limited and affected by several uncertainties, those might be considered supportive of the doses recommended in the lower categories (less than 6 years of age, BSA categories I and II). ORR was consistent across age groups and also with that reported in a larger data set of adults/adolescents.

3.3. Uncertainties and limitations about favourable effects

- The decision to pool the data from various studies due to the rarity of paediatric patients with NTRK/ROS1 fusion-positive tumours and the small sample size is not rejected in principle, as those studies had similar patient populations, dosing regimens, and efficacy endpoints..
- Intrinsic limitations are due to single-arm design, heterogeneity of diseases included in the pooling and small sample size. This also hampers PFS and OS interpretation. However, a SAT can be considered acceptable in this rare paediatric setting.
- Some tumour types can be more indolent (e.g., IMT, infantile fibrosarcoma, low-grade glioma) and others are more aggressive cancers (e.g., high-grade glioma). Therefore, the importance of the uncertainties in the evaluation of the B/R balance, including potential long term safety concerns, could not be established in the overall population at present. Further, also duration of response is of more difficult evaluation in the context of per se indolent diseases. In order to address this limitation, data with longer follow-up of efficacy and safety will be collected in the context of the SOB.

3.4. Unfavourable effects

- Almost all (98.9%) of patients experienced at least one AE, 89.0% of patients experienced at least one AE treatment related to the study drug per the Investigator and 49.5% of patients experienced SAEs (16.5% experienced treatment related SAEs.
- The proportion of patients with AEs leading to treatment discontinuation was 12.1% with fractures as the most frequent reported AE.
- Dose Interruptions and reduction were observed in 41.8% and 24.2% of patients, respectively, with no specific pattern of AEs identifiable. Similar proportions in dose interruption/reduction had been observed in adults/adolescents studies.
- In relation to intensity, no grade 5 AEs were reported and 69.2% of subjects experienced grade 3-4 AEs.
- **SAEs:** a total of 49.5% patients experienced at least one SAE. Fifteen patients (16.5%) experienced at least one treatment-related SAE. Pyrexia (7 patients) followed by pneumonia, femur fracture, hydrocephalus, were the most common ones (5 patients each).
- **Deaths:** in total 20 deaths were reported all classified as due to progression of disease, in the majority of cases the time of occurrence was more than 30 days after last dose of entrectinib.
- **Bone fractures:** A total of 27 out of 91 patients (29.7%) experienced a bone fracture event with the highest frequency in the age range 6-12 years (45.2%). The most frequently occurring ($\geq$5%) serious ADRs in all age groups were fractures (13.2%). Grade 3 events occurred most frequently in the age group $\geq$6 years to $<$12 years (7/31 patients [22.6%]). There were no Grade 4 events. In the majority of cases fractures were resolved, only a minority were reported as unresolved or leading to drug discontinuation. Occurrence is higher in the paediatric age as compared with adults/adolescents (difference of roughly 15%) New evidence from in vitro study on human juvenile or adult bone models, showed that at concentrations lower than the clinical ones entrectinib and M5 dose-dependently decreased osteoblast function and stimulated osteoclastogenesis.

- **Congestive heart failure:** a total of 5 patients (5.5%) experienced CHF events, of whom two patients experienced an event reported as Grade 1 (2.2%) and one patient each (1.1%) experienced events reported as Grade 2, Grade 3, or Grade 4.
- **QT prolongation**: 5.5% patients experienced QT prolongation events 3 patients each (3.3%) had Grade 1 events and two patients (2.2%) had grade 2 events. None of the QT prolongation events in this population was reported as serious or unresolved. Data stratified by ages did not identify a specific trend; overall events were non serious and resolved.

  Neurologic toxicity could be expected in view of the NTRK target distribution in tumour tissues. From study STARTRK-NG a total of 9 cognitive disorders events were reported of which 6 of grade 1, and 2 of grade 2 and 1 of grade 3.

  Infections are more frequently reported in the lowest age ranges (<2 years).

3.5. Uncertainties and limitations about unfavourable effects

- Although due to the rarity of the genetic/molecular subtypes of tumours the size of entrectinib safety database in the claimed indications could be adequate, it is still limited for sound conclusions. The integrated safety population is characterised by a significant heterogeneity including important variables, such as drug formulation, dosing regimen, duration of treatment and tumour type, potentially impacting the safety profile of the drug and increasing the degree of uncertainties related to safety characterization and causality relationship. Moreover, the site and histology independent indication and the uncontrolled design of all the studies included in the analysis are additional limitation to clearly characterize entrectinib-related AEs and potential differences related to underlying malignancies.
- Long-term safety is a missing information and will be provided in the context of the specific obligation.
- **Fractures:** only a partial characterization of this AESI is available since some aspects still remain unclear, such as the role of concurrent risk factors for development of fractures. A direct role of entrectinib on bone fracture risk cannot be excluded due to the impact on physiological bone remodelling processes likely targeting JAK2. Further data to characterize the risk of fractures in paediatric patients (collection of blood markers of bone metabolism and reabsorption, and regularly scheduled DXA scans and hand and knee x-rays) is part of the ongoing integrated safety report from studies STARTRK-2, CO40778 STARTRK-NG, and TAPISTRY as RMP category 3 additional pharmacovigilance activity
- **Congestive heart failure (CHF):** the mechanism underlying CHF in entrectinib-treated patients is currently unknown and the role of risk factors not elucidated yet (occurrence could be observed in subjects with or without classical risk factors).
- **Neurologic toxicity** is clinically rather heterogeneous; assessment of neurologic toxicity is further complicated by the underlying tumour (CNS primary or CNS metastasis) as well as previous treatments (chemotherapy and/or radiotherapy) evoking neurological toxicities. However, although from limited data, it seems that the presence of CNS disease at baseline (including tumour, metastasis) was not related to the occurrence of CNS ADRs, equally distributed between patients with and without CNS

disease; indeed, the presence of baseline disease negatively impacts the severity and outcome of experienced CNS ADRs.

3.6. Effects Table

Table 57: **Effects Table for Rozlytrek in NTRK fusion positive solid tumours in paediatric patients (data cut-off:** 16 July **2023).**

Effect	Short Description	Unit	Treatment	Uncertainties/ Strength of evidence	References
Favourable Effects					
NTRK fusion positive solid tumours in paediatric patients (n=44)					
ORR	ORR (confirmed) per RECIST 1.1/ RANO by BICR	% 95%CI	72.7% (32/44) (57.21, 85.04)	ORR assessed by BICR and confirmed responses/ post-hoc pooled data from single arm studies, limited sample size, different tumour types	
DOR	DOR per RECIST 1.1/ RANO by BICR	Median months 95%CI	NE (25.4, NE)		
Unfavourable Effects (CCOD 16 July 2023) Safety population (n=91)					
total AE AE grade ≥3 SAE AE leading to discontinuation AE leading to death	%		98.9 69.2 49.5 12.1 0	Interpretation of safety hampered by: - Single arm study - differences in exposure, dose, administration regimen, formulation, underlying malignancy, genetics sample size age ranges. No specific trend of ADRs occurrence (including severity grades) across ages with the exception of fractures in particular in the age range 6-12 years and infections (urinary and lung) in the lowest age ranges (0-6 months, 6 months-2 years).	
AESI bone fracture event CHF events QT prolongation Cognitive disorders		%	 29.7 5.5 5.5 8.8		

Abbreviations: ORR: overall response rate; DOR: duration of response; AE: adverse event; AESI: AE of special interest; PT: preferred term; SOC: system organ class.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A pooled analysis of n=44 paediatric subjects with mixed tumour types showing an overall confirmed ORR of 72.7% (95%CI 57.21, 85.04) and median DOR NE, after a median survival follow-up of 24.2 months, supports the sought extension of the NTRK fusion positive solid tumours indication of entrectinib in paediatric patients older that one month and <12 years with no satisfactory treatment options. Although higher ORR was recorded in extracranial solid tumours, responses were also seen in CNS primary cancers. Noting all the limits of an uncontrolled and exploratory dataset, the already approved NTRK indication in adolescent and adults is considered supportive of an extrapolation to lower ages, also considering the similar activity of entrectinib observed in terms of ORR and DOR between the adults and paediatrics pooled datasets as well as in different age ranges within the paediatric setting.

Available safety data in paediatric patients is limited, yet sufficient to allow drawing a conclusion on the benefit risk of entrectinib taking into consideration the rarity of NTRK fusion. The toxicity profile of entrectinib seems overall manageable, granular information on frequency, severity, reversibility of AEs stratified by age ranges has been provided. Although numbers are limited, a specific trend for ADRs occurrence (including severity grades) across ages is not highlighted, with the exception of fractures in particular in the age range 6-12 years and infections (urinary and lung) in the lowest age ranges (0-6 months, 6 months-2 years).

In children between 1 and 6 months of age, while the evidence supporting dose recommendation from a PK perspective are limited, a positive B/R in this population can be concluded based on clinical evidence: indeed 8./10 responders in the NTRK dataset in this age range support keeping younger children (<6 months) in the entrectinib indication. From a safety perspective, SAEs were higher in this age range as compared to older age ranges (>2 years), a specific pattern in distribution of the most relevant ADRs is not noted. Hence, the safety profile in this age range is considered acceptable. Further, a positive B/R balance can be concluded also in the age range 6 months-6 years, where observed PK data, although limited in size and biased by several uncertainties, might be considered of some support of the doses recommended in the lower categories (less than 6 years of age, BSA categories I and II).

3.7.2. Balance of benefits and risks

The efficacy results in terms of ORR and DOR for entrectinib in paediatric patients are overall similar to those shown in the already approved adolescent and adult setting, and are supportive for the sought extension of indication for NTRK fusion positive solid tumours in paediatric subjects older than 1 month of age. These conclusions are based on an uncontrolled and exploratory dataset which require further confirmation of the Benefit-risk post authorisation.

From a safety perspective, the size of the entrectinib database in the claimed indication is limited, however considering the rarity of the genetic/molecular subtypes of tumours, it is considered sufficient to balance the benefits and the risks. A similar safety profile is reported in paediatrics compared with adults/adolescents, with the exception of fractures (in particular 6-12 years old), which impact should be considered.

3.7.3. Additional considerations on the benefit-risk balance

The MAH has discussed the criteria for CMA for the sought indication. In this regard, it is worth noting that Rozlytrek currently holds a conditional marketing authorisation.

a) **Positive B/R**:

The benefit/risk balance is considered positive in the sought indication, as discussed.

b) **It is likely that the applicant will be able to provide comprehensive data**:

The current ongoing SOBs will be used to provide comprehensive data also for the new NTRK paediatric indication (due date 31 March 2027). Based on current enrolment projections, it is estimated that the paediatric NTRK efficacy database will comprise at the due date a total of approximately 64 patients aged <18 years old (i.e. additional 20 patients) with at least 6 months of follow-up, of whom 49 with less than 12 years of age. No amendment is thus proposed to the current NTRK SOB. The increased sample size would also allow to collect further safety data in the paediatric population (approximately 115 entrectinib-treated patients aged ≤ 18 years old are expected in the overall safety database). Based on the expected increased sample size of paediatric patients, together with the data in adult awaited to further confirm the NTRK histology independent efficacy of entrectinib, the CHMP considers that the MAH is likely to provide comprehensive data.

c) **Unmet medical needs will be addressed**:

According to current EU legislation, *"another medicinal product could potentially address the same unmet medical needs (of a conditionally authorized medicinal product), provided it is expected, based on appropriate scientific data, that such a product addresses the unmet medical needs to a similar or greater extent than what is understood for the already conditionally authorised product"* (EMA/CHMP/509951/2006, Rev.1 Guideline on the scientific application on CMA). Therefore, entrectinib in the sought paediatric (>1 month - <12 years) NTRK fusion positive solid tumour indication was to be compared with the also conditionally authorized product Vitrakvi (larotrectinib) holding an overlapping indication.

Considering the limit of indirect comparison of the safety of two different products based on different single arm datasets (n=91 for entrectinib, n=94 for larotrectinib), it remains that a higher incidence of fractures in the paediatric population was reported (30% vs 9%) in entrectinib as compared to larotrectinib. However other factors, e.g. possible different fracture monitoring, different median age in the two paediatric datasets (median age 6 y in entrectinib and 2.2 y in larotrectinib, given a risk of bone fracture higher for entrectinib in the 6-12y age range) could partially explain such difference.

Uncertainties remain on whether fracture could be a class-effect related to NTRK inhibition, or if the additional JAK2 inhibition observed with entrectinib could play a role. Due to all the uncertainties above, the magnitude of such safety issue cannot be definitively concluded. The risk of fracture is under comprehensive scrutiny through a category 3 ongoing additional pharmacovigilance activity for entrectinib [i.e. Integrated safety analysis report to assess risk of fracture based on STARTRK-2, STARTRK-NG, an TAPISTRY studies].

On the other hand, the available data might be suggestive of a potential higher activity of entrectinib in CNS disease as compared with larotrectinib: indeed, clinical data in paediatric subjects with NTRK+ primary CNS tumours, although still in a limited number of patients (n=20 for entrectinib and n=26 for larotrectinib), showed a trend toward better ORR point estimates (60% vs 38%), further supported by non-clinical data (greater CNS penetration with entrectinib in animal model). However, due to the limit of indirect comparison together with

the limited number of paediatric patients with CNS primary disease, it is not possible to make definitive conclusion at present on the demonstration of this advantage.

In conclusion, taking into account the accumulated clinical data and residual uncertainties so far for entrectinib in comparison with larotrectinib it is agreed that there is a potential higher risk of fracture but also a potential higher activity of entrectinib in CNS disease as compared with larotrectinib. Thus, overall, entrectinib can be expected to address the unmet medical need to a similar extent than what is understood for the already conditionally authorised larotrectinib.

d) The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

There is an unmet need for tolerable targeted therapeutic options for patients with NTRK fusion-positive tumours, particularly for paediatric patients including for those with CNS tumours.

Given the positive benefit/risk balance for entrectinib, the current unmet medical need, and the fact that additional data will be collected and provided to confirm the benefit/risk balance in paediatric patients, the benefits to public health of immediate availability outweigh the risks inherent in the fact that additional data are still required.

3.8. Conclusions

The overall benefit/risk balance of entrectinib in the sought paediatric NTRK positive solid tumours indication who have no alternative treatment options in the age over 1 month – 12 years is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Rozlytrek is not similar to burosumab, dinutuximab beta, tebentafusp, lutetium (177Lu), avapritinib, cabozantinib, sorafenib tosylate, irinotecan hydrochloride trihydrate, pemigatinib, ripretinib, ivosidenib, niraparib, dabrafenib, trametinib and retifanlimab within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus the granting of an extension of the marketing authorisation for the above-mentioned medicinal product concerning:

a new pharmaceutical form: coated granules associated with a new strength (50 mg);

a new route of administration: (gastroenteral use) for the already authorised 100 mg and 200 mg hard capsules presentations.

In addition, the CHMP recommends the variation to the terms of the marketing authorisation, concerning the following change:

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

- C.I.6.a - Extension of the currently approved indication of Rozlytrek in solid tumours with NTRK gene fusion to patients from 1 month to 12 years of age (both for the coated granules and already approved hard capsules presentations).
Based on final results from studies CO40778 (STARTRK-NG), GO40782 (STARTRK-2) and BO41932 (TAPISTRY). Study CO40778 is a Phase I/II open-label, dose-escalation and expansion study of entrectinib in paediatrics with locally advanced or metastatic solid or primary CNS tumours and/or who have no satisfactory treatment options; Study GO40782 is an open-label, multicenter, global Phase II basket study of entrectinib for the treatment of patients with solid tumours that harbour an NTRK1/2/3, ROS1, or ALK gene rearrangement (fusion), and Study BO41932 is a Phase II, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in participants with unresectable, locally advanced or metastatic solid tumours determined to harbour specific oncogenic genomic alterations or who are tumour mutational burden (TMB)-high as identified by a validated next-generation sequencing (NGS) assay. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated.

- C.I.4. - Addition of wording regarding the possibility to prepare a suspension in water of the content of the capsules to be used orally or via the e.g., gastric or nasogastric tube. As a consequence, sections 4.2, 5.2, 6.3, 6.4 and 6.6 of the SmPC are updated.

The Package Leaflet and Labelling are updated in accordance.

The RMP (version 5.2) is updated in accordance.

The MAH took the opportunity to introduce minor editorial changes to the PI and to update Annex II of the SmPC.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Rozlytrek subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and

interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
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
In order to further investigate the impact of the presence/absence of other molecular alteration on the efficacy of entrectinib, the MAH should submit the results from tumour genomic profiling by plasma and/or tissue when possible at baseline and progression together with clinical outcomes association per tumour histology for the patients from the updated pooled analysis.	31 March 2027

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0351/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.