28 May 2020
EMA/379739/2020
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Rozlytrek

International non-proprietary name: entrectinib

Procedure No. EMEA/H/C/004936/0000

Note

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

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List of abbreviations

5-HT	5-hydroxytryptamine (serotonin)
ADR	adverse drug reaction
AE	adverse event
ALK	Anaplastic Lymphoma Kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the plasma concentration versus time curve
AUC0-24 or AUC0-t	area under the concentration-time curve from time zero to 24 hours post entrectinib dose (or throughout the once-daily dosing interval, tau)
AUCinf	area under the plasma concentration-time curve from time zero to infinity, calculated by extrapolation from AUClast
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BICR	blinded independent central review
BLQ	below limit of quantitation
BOR	best overall response
BSA	body surface area
BTD	Breakthrough Therapy Designation
CAP	College of American Pathologists
CB	cannabinoid
CBR	clinical benefit rate
CCOD	clinical cut-off date
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	apparent total plasma clearance, estimated by Dose/AUC0-∞, where F is oral bioavailability
CLIA	Clinical Laboratory Improvement Amendments
CMA	Conditional Marketing Approval
Cmax	maximum measured plasma concentration
CNS	central nervous system
CoA	certificate of analysis

COX2	cyclooxygenase-2
CPP	Critical process parameter
CQA	Critical Quality Attribute
CR	complete response
CSP	crystal structure prediction
CT	computed tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
ctDNA	circulating tumour DNA
Ctrough	trough analyte concentration in the plasma
CV	Coefficient of variation
CYP	cytochrome P450
D	dopamine
DLT	dose-limiting toxicities
DoE	Design of experiments
DOR	duration of response
DSC	Differential Scanning Calorimetry
DVS	Dynamic vapor sorption
EC	European Commission
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCTD	electronic Common Technical Document
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EORTC-QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ERA	Environmental Risk Assessment
EXPT	Experiment
F	bioavailability
F1CDx	Foundation One companion diagnostic test
FDA	Food and Drug Administration (US)
fe	fraction excreted unchanged in urine
Fg	fraction that escapes intestinal first-pass metabolism

FH EMR	Flatiron Health Electronic Medical Record
FISH	fluorescence in situ hybridization
FMI	Foundation Medicine, Inc.
fu	fraction unbound
GC	Gas Chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GR	glucocorticoid receptor
GTI	Genotoxic impurity
H	histamine
HDPE	High Density Polyethylene
hERG	human Ether-à-go-go-related Gene
HNSCC	Head and neck squamous cell carcinoma
HPLC	High performance liquid chromatography
HPMC	hydroxypropyl methylcellulose
IC50	Median inhibitory concentrations
IC-DOR	intracranial duration of response
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IC-ORR	intracranial objective response rate
IC-PFS	intracranial progression-free survival
ICP-MS	Inductively coupled plasma mass spectrometry
IFS	infantile fibrosarcoma
IHC	immunohistochemistry
ILD	interstitial lung disease
IMT	inflammatory myofibroblastic tumour
IND	Investigational New Drug
INN	International Nonproprietary Name
IPC	In-process control
IR	Infrared
IU	International Units
kel	apparent terminal elimination rate constant
KG	tumour (re-)growth rate
KM	Kaplan-Meier

KS	tumour shrinkage rate
LC	Liquid chromatography
LC/MS/MS	liquid chromatography with tandem mass spectrometry
LDPE	Low Density Polyethylene
LLOQ	lower limit of quantitation
LMS	leiomyosarcoma
LOD	Limit of detection
LOQ	Limit of quantification
M	Acetylcholine receptor (muscarinic)
M/P	metabolite-to-parent ratio
MA	Material attributes
MAA	Marketing Authorisation Application
MASC	Mammary analogue secretory carcinoma
MRI	magnetic resonance imaging
MS	Mass Spectrometry
MTD	maximum tolerated dose
NA	not applicable
NCA	non-compartmental analysis
NGF	nerve growth factor
NGS	next generation sequencing
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NRG	Name Review Group
NSCLC	non-small cell lung cancer
NTRK1/2/3	Neurotrophic Tyrosine Receptor Kinase 1/2/3
ODD	Orphan Drug Designation
OFAT	one-factor-at-a-time
ORR	overall response rate
OS	overall survival
OX	Orexin
PAR	Proven Acceptable Range
PBPK	physiologically-based PK
PDCO	Paediatric Committee

PDX	patient-derived xenograft
PFS	progression-free survival
P-GP	Permeability-glycoprotein
P-gp	P-glycoprotein 1
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PP	process parameters
PPARɣ	Peroxisome proliferator-activated receptor gamma
PPI	proton pump inhibitor
PR	partial response
PSMF	Pharmacovigilance System Master File
PXRD	Powder X-ray diffractometer.
QbD	Quality by design
QC	Quality Control
QD	once a day
QPPV	Qualified Person responsible for Pharmacovigilance
QTPP	Quality target product profile
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumours
RH	Relative Humidity
RH	Relative Humidity
RMP	Risk Management Plan
ROS1	Proto-oncogen tyrosine-protein kinase 1
RP2D	Recommended Phase II dose
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBC	secretory breast carcinoma
SCID	Severe combined immunodeficiency
SD	stable disease
SLD	sum of longest diameters
SmPC	Summary of Product Characteristics

SMQ	standard MedDRA query
SOC	System Organ Class
SRS	stereotactic radiosurgery
SST	Somatostatin
STAT3	Signal transducer and activator of transcription 3
STS	soft tissue sarcoma
t½	apparent terminal elimination half-life
TAMC	Total Aerobic Microbial Count
TCXRPD	temperature-controlled X-ray powder diffraction
TGA	Thermo-Gravimetric Analysis
TGI	Tumour growth inhibition
TKI	tyrosine kinase inhibitor
Tmax	time of the maximum measured plasma concentration
TRK	Tropomyosin receptor kinase
TRKA/B/C	Tropomyosin Receptor Kinases A/B/C
TYMC	Total Combined Yeasts/Moulds Count
ULN	upper limit of normal
UV	Ultraviolet
V/F	apparent oral volume of distribution
VEGF	vascular endothelial growth factor
Vis	Visible
Vz/F	apparent volume of distribution during the elimination phase after oral administration
WBRT	whole-brain radiotherapy
WHO	World Health Organization
WHOCC	WHO Collaborating Centre
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration GmbH submitted on 7 January 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Rozlytrek, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 October 2017.

Rozlytrek was granted eligibility to PRIME on 13 October 2017 in the following indication: treatment of neurotrophic tyrosine receptor kinase (NTRK) fusion-positive, locally advanced or metastatic solid tumours in adult and paediatric patients who have either progressed following prior therapies or who have no acceptable standard therapy.

Eligibility to PRIME was granted at the time in view of the following:

- Due to the lack of historical data in the patients with NTRK fusion-positive tumours, data are presented and discussed regardless of NTRK status. Considering the broad cancer types that may be suitable for treatment with entrectinib, unmet medical need was assessed for tumour types in which *NTRK* fusions have been observed to date. Overall these cancers present poor prognosis and significant levels of aggressiveness and mortality. The unmet medical need was recognised.
- Available nonclinical data were adequately supportive of the mechanism of action and potential activity across different tumour types.
- Preliminary data in 26 adult patients with NTRK fusion-positive solid tumours showed an ORR in 17/26 (65.4%) of patients supportive of promising activity. Responses were observed in most pre-treated patients (up to 4 prior lines of treatment) and in a range of heterogeneous histologies (sarcomas, NSCLC, cholangiocarcinoma, pancreatic).
- Despite the lack of historical data in biomarker-positive, this compared favourably with historical data in biomarker unrestricted 2+ line patients with included tumour types.
- Overall, this supported the potential for this therapeutic option to represent a major therapeutic advantage, at least for a subset of patients for whom an unmet need is likely undisputable (advanced stage with no available treatments).

The applicant applied for the following indication:

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive locally advanced or metastatic solid tumours, who have progressed following prior therapies or as initial therapy when there are no acceptable standard therapies.

Rozlytrek as monotherapy is indicated for the treatment of patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0010/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0010/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Applicant's requests for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14(9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance entrectinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

PRIME support

Upon granting of eligibility to PRIME, Daniela Melchiorri was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 5 February 2018. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

Selection of regulatory starting materials, control strategy for active substance and drug product, stability data and plans, strength of available nonclinical evidence to support histology independent NTRK clinical indication, plans for generation of additional nonclinical evidence, criteria for selection of the target population and plans for collection of historical data on prognosis of patients with NTRK fusion mutations, proposed confirmatory data, ROS-1 development strategy, paediatric investigation plan.

Scientific advice

The applicant received Scientific Advice from the CHMP on the development for the indication from the CHMP on 22 October 2015 EMEA/H/SA/3140/1/2015/SME/III), 20 July 2017 (EMEA/H/SA/3140/2/2017/SME/II), 09 November 2017 (EMEA/H/SA/3140/3/2017/SME/II, EMEA/H/SA/3140/2/FU/1/2017/SME/II and EMEA/H/SA/3140/4/2017/SME/I), 26 July 2018 (EMEA/H/SA/3140/FU/1/2018/PR/I).

The Scientific Advice pertained to the following quality, non-clinical, and clinical aspects:

- Proposals for drug substance starting materials, impurities qualification, control strategy, stability data, process validation; drug product dissolution method, manufacturing control strategy, stability plan, registration pilot scale; in vitro analytical comparison plan to bridge from drug product clinical development lots to the commercial registration lots;
- Adequacy of the non-clinical program to support a Marketing Authorisation Application (MAA) for entrectinib;
- Proposal for clinical pharmacology characterisation, including the ADME profile; CYP drug-drug interaction (DDI), intrinsic factors and effects on QT assessments;
- The use of a basket trial design (STARTRK-2) to support registration in multiple tumour types/gene arrangements; the suitability of a two-step assay (IHC followed by NGS) for identifying patients for enrolment in STARTRK-2; the use of ORR as primary endpoint; whether a response rate of 20% would be considered a clinically meaningful benefit; the proposed primary and secondary efficacy analyses; the sample size requirements for the three NTRK genotypes in the study; the suitable type of Marketing Authorisation for non-conventional clinical programme;
- The pooling of data across studies ALKA-372-001, STARTRK-1, STARTRK-2, and STARTRK-NG; the adequacy of the key statistical assumptions to support the evaluation of the efficacy of entrectinib in the ROS1 fusion-positive, ROS1 inhibitor-naïve, NSCLC patient population; the size of the safety database for the pooled safety data from studies ALKA-372-001, STARTRK-1, and STARTRK-2.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Melchiorri Co-Rapporteur: Filip Josephson

The application was received by the EMA on	7 January 2019
The procedure started on	30 January 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	2 May 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	30 April 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	6 May 2019

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	29 May 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	23 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	17 October 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of outstanding issues to all CHMP members on	29 November 2019
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	12 December 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 May 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positiveopinion for granting a marketing authorisation to Rozlytrek on	28 May 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The Applicant is seeking the approval of two separate therapeutic indications for Entrectinib:

- adult and paediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive locally advanced or metastatic solid tumours, who have progressed following prior therapies or as initial therapy when there are no acceptable standard therapies.

- patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC).

2.1.2. Epidemiology and risk factors, screening tools/prevention

NTRK fusion positive solid tumours

NTRK fusions are rare events in common adult cancers, e.g. frequency of <1% in NSCLC and 1-2% in CRC, and more frequently observed in some rare cancers, e.g. 90-100% in mammary analogue secretory carcinoma (MASC), a rare form of salivary gland cancer (representing <1% of all cancer malignancies), and secretory breast cancer (SBC), for which NTRK fusion expression (ETV6-NTRK3) is a pathognomonic hallmark for both diseases[1].

NTRK fusions have also been described in several pediatric tumours including infantile fibrosarcoma (IFS) or the related congenital mesoblastic nephroma (for which the ETV6-NTRK3 fusion is also a characteristic feature), and with high frequency (~40%) in high grade glioma in patients <3 years of age[2].

The overall prevalence of NTRK fusions in all cancer patients is estimated to be 0.25-1%[345].

1 Kheder ES, Hong DS. Emerging targeted therapy for tumors with NTRK fusion proteins. Clin Cancer Res. 2018.
2 Wu G, Diaz AK, Paugh BS, et al. The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nature Genet. 2014;46:444-450.
3 Stransky, N., Cerami, E., Schalm, S., Kim, J. L. & Lengauer, C. The landscape of kinase fusions in cancer. Nat. Commun. 5, 4846(2014).
4 Vaishnavi, A., Le, A. T. & Doebele, R. C. TRKing down an old oncogene in a new era of targeted therapy. Cancer Discov. 5, 25–34 (2015).
5 Drilon, A. et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N. Engl. J. Med. 378, 731–739 (2018).

Table 1: Incidence of NTRK gene fusions across multiple solid tumour histologies in adult and paediatric patients

Tumor Histology	NTRK1	NTRK2	NTRK3	Present in Pediatric Tumors
Astrocytoma		3%[a]		Y
Breast (secretory)			92%[b]	Y
Cholangiocarcinoma	4%[c]			N
Congenital fibrosarcoma			90–100%[d]	Y
Colorectal carcinoma	1–2%[e]		1%[f]	N
Glioblastoma	1–6%[g]			Y
Head and neck cancer		<1%[f]	<1%[f]	Y
Inflammatory myofibroblastic tumors			3%[h]	Y
Spitzoid melanoma	21%[i]			Y
Mesoblastic nephroma			83%[d]	Y
Myosarcoma	1%[f]			Y
Non-small cell lung cancer	1–3%[j]	<1%[f]		N
Papillary thyroid	5–13%[k]		2–24%[l]	Y
Pediatric sarcomas	<1%[m]			Y
Pediatric glioma	2–3%[n]	1–2%[n]	<1%[n]	Y
Salivary gland: Mammary analog secretory carcinoma			90–100%[o]	N
Salivary gland: Not otherwise specified			2%[p]	N

N = no; Y = yes.

a: Jones et al. 2013; b: Tognon et al. 2002; c: Ross et al. 2014; d: Rubin et al. 1998; e: Martin-Zanca et al. 1986, Ardini et al. 2014; f: Stransky et al. 2014; g: Frattini et al. 2013, Kim et al. 2014; h: Yamamoto et al. 2015; i: Weisner et al. 2014; j: Vaishnavi et al. 2013; k: Greco et al. 2010; l: Leeman-Neill et al. 2014, Ricarte-Filho et al. 2013, Prasad et al. 2016; m: Morosini et al. 2015; n: Wu et al. 2014; o: Knezevich et al. 1998; p: Weinreb et al. 2013.

ROS1-positive advanced NSCLC

Lung cancer is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths)[6]. NSCLC accounts for more than 80% of all lung cancer cases, that include non-squamous (i.e, adenocarcinoma, large-cell carcinoma, and other cell types) and squamous cell carcinoma. Nearly half of all lung cancers is adenocarcinoma. Over the last decades, in Europe squamous NSCLC decreased while adenocarcinoma has increased in men, while in women both squamous NSCLC and adenocarcinoma are still increasing[7].

In recent years, a number of molecular alterations have been identified in NSCLC, leading to the development and approval of targeted therapies with specific tyrosine kinase inhibitor (TKI) activity, such as erlotinib, afatinib, gefitinib, osimertinib and dacomitinib for epidermal growth factor receptor (EGFR) mutations; crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib for ALK gene fusions, crizotinib for ROS1 gene fusions, and dabrafenib in combination with trametinib for BRAF V600 mutation.

[6] Bray F et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.
[7] Forman D et al. editors (2014). Cancer Incidence in Five Continents, Vol. X. IARC Scientific Publication No. 164. Lyon: International Agency for Research on Cancer.

In general, the mutations/alterations are seen in a non-overlapping fashion, although between 1%-3% harbour concurrent alterations[8]. According to current guidelines, EGFR, ALK, ROS1 and BRAF V600 should be tested in advanced non-squamous NSCLC. Molecular EGFR and ALK testing are not recommended in patients with a confident diagnosis of SCC, except in unusual cases, e.g. never/former light smokers or long-time ex-smokers[9].

Development of immune checkpoint inhibitors targeting PD-1/PD-L1, as monotherapy and in combination with chemotherapy, has recently led to major changes in the treatment paradigm for patients with advanced NSCLC over the last few years.

2.1.3. Biologic features, Aetiology and pathogenesis

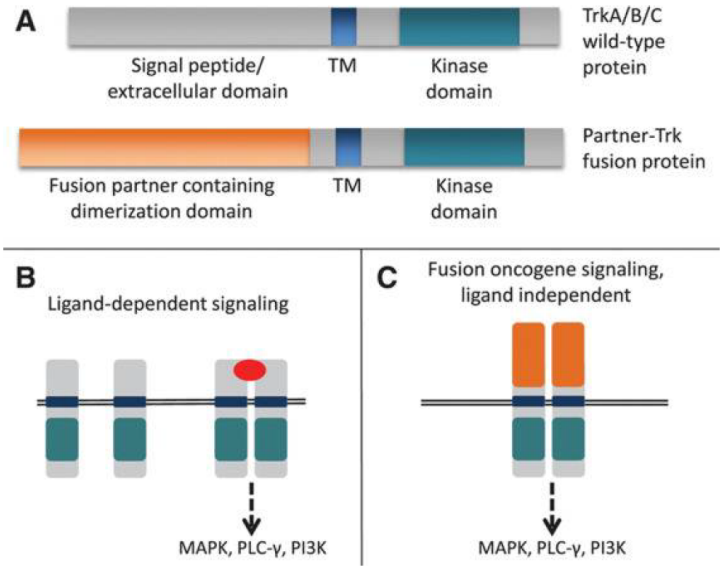
NTRK fusion positive solid tumours

The neurotrophic receptor tyrosine kinase family of genes NTRK1, NTRK2, and NTRK3 encode the tropomyosin receptor kinases A, B and C (TRKA, TRKB and TRKC), respectively. TRK family members are transmembrane proteins serving as high affinity signal transducing receptors for neurotrophins. They are expressed in neuronal tissue and play an essential physiological role in the development and function of the central and peripheral nervous systems. TRKA binds nerve growth factor (NGF), TRKB binds brain-derived growth factor (BDNF) and neurotrophin-4 (NT4, also known as NTF5) with high affinity and neurotrophin-3 (NT3) to a lesser extent and TRKC binds NT3. 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 sequences10. 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 apoptosis.

At least 25 different oncogenic NTRK1/2/3 gene fusions have been reported across at least 11 specific tumour types[11] [12].

8 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer Version 3.2019 — January 18, 2019
9 Planchard D et al. Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol (2018) 29 (suppl 4): iv192–iv237.
10 Khotskaya YB, Holla VR, Farago AF, et al. Targeting TRK family proteins in cancer. Pharmacol Ther. 2017;173:58-66.
11 Kheder ES, Hong DS. Emerging targeted therapy for tumors with NTRK fusion proteins. Clin Cancer Res. 2018.
12 Lange AM, Lo HW. Inhibiting TRK Proteins in Clinical Cancer Therapy. Cancers (Basel). 2018;10. pii: E105.



(A) Schematic diagrams showing the wild-type TRKA/B/C protein (top) and an oncogenic fusion involving a partner gene that contains a dimerization domain and the kinase domain of TRKA/B/C (bottom).

(B) In the absence of ligand (left), TRK proteins do not dimerize or activate downstream pathways. In the presence of ligand (red oval), TRK proteins dimerize, leading to downstream pathway activation. The double line represents the cell membrane.

(C) Fusion oncogenes dimerize in a ligand-independent manner, leading to constitutive activation and downstream signaling.

Note: Proteins and their domains are not drawn to scale.

Source: Farago et al. 2015.

Figure 1: TRKA/B/C (NTRK1/2/3) fusion structure and resultant signalling

ROS1-positive advanced NSCLC

The ROS proto-oncogene 1 (ROS1), located on chromosome 6, encodes an orphan receptor tyrosine kinase without a known ligand, whose physiological function is still unclear. Chromosomal translocations can result in ROS1 gene rearrangements, firstly reported in NSCLC in 2007, characterised by fusions with other genes. So far, 22 different fusion partner genes have been identified in lung cancer patients[13], being CD74-ROS1 fusion the most common rearrangement. These fusion events lead to constitutive activation of the ROS1 kinase that drives cellular transformation and promotes survival and proliferation through downstream signaling via SHP-1/SHP-2, JAK/STAT, PI3K/AKT/MTOR and MAPK/ERK pathways. ROS1 rearranged NSCLC has been described as a distinct molecular type in approximately 1–2% of patients with NSCLC[14].

2.1.4. Clinical presentation, diagnosis and stage/prognosis

NTRK fusion positive solid tumours

At the time that the entrectinib development program was initiated, there were limited publicly available data on the outcomes of patients specifically with NTRK fusion-positive tumours.

Reported below some data regarding the tumour types characterized by high prevalence (>90%) of NTRK gene fusion:

13 Ou S et al. CNS metastasis in ROS1+ NSCLC: An urgent call to action, to understand, and to overcome. Lung Cancer 2019(130):201–207.
14 Lin JJ, Shaw AT. Recent Advances in Targeting ROS1 in Lung Cancer. J Thorac Oncol. 2017 Nov; 12(11):1611-1625.

Mammary Analogue Secretory Carcinoma (MASC): this is a salivary gland malignancy. Standard optimised treatment for MASC is not well defined; most studies in the literature are retrospective[15]. Current treatment is similar to other salivary gland malignancies with surgical excision being the primary approach, alone or with post-operative radiotherapy[16]. While usually a low grade malignancy, high-grade transformation of MASC has been described. Aggressive salvage surgery is recommended in the context of managing metastatic salivary gland tumours, given the morbidity associated with tumour progression and the lack of significant response associated with other available treatment modalities. Various chemotherapy regimens have displayed modest response rates with unclear survival advantages in patients with metastatic salivary gland cancer.

Secretory Breast Cancers (SBCs): This is a very rare type of breast cancer, generally associated with a favorable prognosis, although having triple-negative phenotype. There are no consensus guideline recommendations for treatment of SBC. Most SBC cases are treated in a manner similar to invasive ductal carcinoma with surgical resection being the primary means of treatment, although the extent of surgery ranges from wide local excision only to radical mastectomy depending on the age of the patient and technical difficulties of breast conservation (e.g. in young children)[17]. The use of systemic chemotherapy and radiotherapy for the treatment of secretory breast cancer varies across the literature. Radiotherapy is usually used in adults following breast-conserving surgery[18] while limited data support the use of hormone therapy (for hormone-positive secretory breast tumours) or chemotherapy in cases with poorly circumscribed tumours[19].

Congenital Infantile fibrosarcoma: Congenital infantile fibrosarcoma (CIFS) is a rare mesenchymal tumour that is primarily developed in the soft tissue of distal extremities, accounting for 10% of STS in children, and usually occurring in the first year of life. Surgery is the treatment of choice for the majority of cases where IFS remains localised and is associated with a good prognosis. Complete non-mutilating resection is rarely feasible, and chemotherapy in the neoadjuvant setting has been demonstrated to be effective in reducing tumour size to allow conservative surgery[20]. The chemotherapy combination of vincristine and actinomycin D is the most commonly used and is absent of the toxicities in infants associated with alkylating agents or anthracyclines. Despite good control in many patients with initial surgery and chemotherapy, the clinical course can be aggressive for some patients with local recurrences and metastatic spread requiring multiple additional surgeries and adjuvant chemotherapy or radiotherapy.

ROS1-positive advanced NSCLC

ROS1 and ALK tyrosine kinase domains also share significant homology, including bindings sites for ATP and crizotinib. Similarly to ALK rearranged tumours, patients with ROS1 positive NSCLC are more commonly of younger age, have history of never or light smoking, and have adenocarcinoma histology[21]. However, ROS1-rearranged NSCLC was described to have significantly lower rates of

15 Bishop J. Unmasking MASC: bringing to light the unique morphologic, immunohistochemical and genetic features of the newly recognized mammary analogue secretory carcinoma of salivary glands. Head Neck Pathol. 2013;7:35–39.
16 Boon E, Valstar MH, van der Graaf WTA, et al. Clinicopathological characteristics and outcome of 31 patients with ETV6-NTRK3 fusion gene confirmed (mammary analogue) secretory carcinoma of salivary glands. Oral Oncol. 2018;82:29-33.
17 Cadoo KA, McArdle O, O'Shea AM, et al. Management of unusual histological types of breast cancer. Oncologist. 2012;17:1135-45.
18 Horowitz DP, Sharma CS, Connolly E, et al. Secretory carcinoma of the breast: results from the survival, epidemiology and end results database. Breast. 2012;21:350-353.
19 Garlick JW, Olson KA, Downs-Kelly E, et al. Secretory breast carcinoma in an 8-year-old girl: A case report and literature review. Breast J. 2018;24:1055-1061.
20 Orbach D, Rey A, Cecchetto G, et al. Infantile fibrosarcoma: management based on the European experience. J Clin Oncol. 2010;28:318-323.
21 Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol. 2012;30:863-870.

extra-thoracic and intracranial metastases at the time of diagnosis, as well as lower cumulative incidence of intracranial metastases[22], although a subsequent single institution retrospective study described similar rates of intracranial metastases at diagnosis among patients with ALK and ROS1 rearranged lung cancers[23]. CD74-ROS1 fusion variant was found to increase the predilection for CNS metastasis compared to non-CD74-ROS1 fusion variant[24]. Overall, the incidence of brain metastases from prospective trials of ROS1 TKIs ranged approximately from 20% to 40% in TKI-naïve patients and from 30% to 50% in TKI-pretreated patients[25].

Commonly used methods for ROS1 fusion detection have included fluorescence in situ hybridization (FISH), immunohystochemistry (IHC), reverse-transcription polymerase chain reaction (RT-PCR) and next generation sequencing (NGS). According to ESMO guidelines, IHC may be used as a screening approach, although it is currently not recommended as the primary treatment determining test. FISH has been the standard approach to detecting ROS1 rearrangements. NGS is an emerging technology. Multiplex, massively parallel, so-called next-generation sequencing (NGS) of various sorts is rapidly being adopted as the standard approach to screening adenocarcinomas for oncogenic targets. Whatever testing modality is used, it is mandatory that adequate internal validation and quality control measures are in place and that laboratories participate in, and perform adequately in, external quality assurance schemes for each biomarker test[26]. RT-PCR assays may lead to under-detection of ROS1 fusion events as miss the detection of previously unknown fusion partners. For comparison, NGS allows for the detection of known as well as novel fusions[27].

With more than one detection methodology now available, there will be an increasing number of cases where they produce conflicting test results, posing a diagnostic and therefore therapeutic challenge. Additionally, recent studies with multiregion sequencing have shown significant tumour heterogeneity with subclone-specific mutations, although none of these studies investigated the clonal nature of ALK or ROS1[28][29].

2.1.5. Management

NTRK fusion positive solid tumours

The proposed indication for the use of entrectinib in this application is for patients with NTRK fusion-positive locally advanced or metastatic solid tumours who have progressed following prior therapies or as initial therapy when there are no acceptable standard therapies. The prognosis for these patients is poor, particularly when there is CNS involvement. Expected response rates to later lines of treatment in this setting are typically <30% and median duration of response (mDOR) <10 months across available approved agents for various tumour types. Patients who have exhausted these options or patients with tumours for which no standard or approved option is available, receive best supportive care or are entered into Phase I clinical trials where the expected response rates are ≤10%.

22 Gainor JF et al. Patterns of Metastatic Spread and Mechanisms of Resistance to Crizotinib in ROS1-Positive Non-Small-Cell Lung Cancer. JCO Precis Oncol. 2017.
23 Patil T et al. The Incidence of Brain Metastases in Stage IV ROS1-Rearranged Non-Small Cell Lung Cancer and Rate of Central Nervous System Progression on Crizotinib. J Thorac Oncol. 2018 Nov; 13(11):1717-1726.
24 Z. Li, L. Shen, D. Ding, et al., Efficacy of crizotinib among different types of ROS1 fusion partners in patients with ROS1-rearranged non-small cell lung cancer, J. Thorac. Oncol. 13 (2018) 987–995.
25 Ou S et al. CNS metastasis in ROS1+ NSCLC: An urgent call to action, to understand, and to overcome. Lung Cancer 130 (2019) 201–207.
26 Planchard D et al. Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol (2018) 29 (suppl 4): iv192–iv237.
27 Lin J et al. Recent advances in targeting ROS1 in lung cancer. J Thorac Oncol 2007;12(11):1611-1625.
28 Jamal-Hanjani M et al. Tracking the Evolution of Non-Small-Cell Lung Cancer. N Engl J Med 2019;376:2109-2121
29 Sun TY et al. Tumor heterogeneity and testing discrepancy confound ROS1 detection in NSCLC. Journal of Thoracic Oncology Available online 23 March 2019 In Press.

In September 2019, the NTRK inhibitor larotrectinib was granted conditional marketing authorisation in the EU for the treatment of adult and paediatric patients with solid tumours that display 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 no satisfactory treatment options, based on an pooled primary analysis set for efficacy including 93 patients with TRK fusion-positive cancer enrolled across 3 ongoing open-label single arm studies (of those, 28 patients were pediatric), and additional 9 subjects with primary CNS disease. The ORR in the pooled efficacy dataset was 72% (95%CI 62, 81), with 16% of CR. Median DOR was NR (range 1.6+, 38.7+) with 88% with duration more than 12 months. Among 5 evaluable patients with non-primary CNS tumor with brain metastases, 3 had PR (2 thyroid, 1 lung) and 2 had SD (lung); overall ORR was 60% (95% CI: 15-95).

The safety of Larotrectinib was evaluated in 125 patients with TRK fusion-positive cancer. The most common adverse drug reactions (≥ 20%) of Vitrakvi were fatigue (32%), increased ALT (31%), dizziness (30%), increased AST (29%), constipation (29%), nausea (26%), anaemia (24%), and vomiting (20%). The majority of adverse reactions were Grade 1 or 2. Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (1.6%) and ALT increased (< 1%). The highest reported grade was Grade 3 for adverse reactions anaemia, weight increased, fatigue, increased AST, dizziness, paraesthesia, nausea, myalgia, and leukocyte count decreased. All the reported Grade 3 adverse reactions occurred in less than 5% of patients, with the exception of anaemia (7%). Permanent discontinuation of Vitrakvi for treatment emergent adverse reactions, regardless of attribution occurred in 3% of patients. (Vitrakvi EU SmPC, Vitrakvi EPAR).

Table 2: Overall response rate and duration of response by tumour type

Tumour type	Patients (n=102)	ORR		DOR	
		%	95% CI	≥ 12 months	Range (months)
Soft tissue sarcoma[a]	21	81%	58%, 95%	78%	1.9+, 38.7+
Salivary gland[a]	17	88%	64%, 99%	91%	3.7+, 33.7+
Infantile fibrosarcoma[a]	13	92%	64%, 100%	60%	1.6+, 17.3+
Thyroid[a]	10	70%	35%, 93%	86%	3.7, 29.8+
Primary CNS[b]	9	11%	0%, 48%	NR	2.0+
Lung[a]	7	71%	29%, 96%	75%	7.4+, 25.8+
Melanoma[a]	7	43%	10%, 82%	50%	1.9+, 23.2+
Colon[a]	6	33%	4%, 78%	NR	5.6, 9.2+
Gastrointestinal stromal tumour[a]	4	100%	40%, 100%	67%	7.4+, 20.0+
Bone sarcoma[a]	2	50%	1%, 99%	0%	9.5
Cholangiocarcinoma[a]	2	SD, NE	NA	NA	NA
Congenital mesoblastic nephroma[a]	1	100%	3%, 100%	NR	9.8+
Appendix[a]	1	SD	NA	NA	NA
Breast[a, c]	1	PD	NA	NA	NA
Pancreas[a]	1	SD	NA	NA	NA

DOR: duration of response
NA: not applicable due to small numbers or lack of response
NE: not evaluable
NR: not reached
PD: progressive disease
SD: stable disease
+ denotes ongoing response
[a] independent review committee analysis by RECIST v1.1
[b] patients with a primary CNS tumour were evaluated per investigator assessment using either RANO or RECIST v1.1 criteria
[c] non-secretory

Table 3: Efficacy of approved or available therapies for patients with tumour types reported to harbour NTRK fusions and who have either progressed following prior therapies or who have no acceptable standard therapies

	Therapy	Line of treatment	ORR (%)	mDOR (months)	mPFS (months)	mOS (months)	Reference
Non Small-Cell Lung Cancer (EGFR or ALK negative)	Docetaxel	2L	6.8	6.0	2.8 (TTP)	7.9	Shepherd et al. 2000
	Pemetrexed	2L	9.1	4.6	2.9	8.3	Hanna et al. 2004
	Bevacizumab+Paclitaxel	2L or 3L	22.5	NA	5.4	9.9	Cortot et al. 2016
	Docetaxel+Ramucirumab	2L	22.9	NA	4.5	10.5	Garon et al. 2014
	Pembrolizumab[a]	≥2L	18.5	NR	4.0	12.7	Herbst et al. 2016
	Docetaxel+Nintedanib	2L	4.7	NA	3.4	12.6	Reck et al. 2014
	Nivolumab	≥2L	19.2	17.2	2.3	12.2	Borghaei et al. 2015
Colorectal Carcinoma	Cetuximab+Irinotecan[b]	2L	16.4	5.7	4.0	10.7	Sobrero et al. 2008
	Panitumumab+FOLFIRI[b]	2L	35.4	7.6	5.9	14.5	Peeters et al. 2010
	Bevacizumab+FOLFOX-4	2L	22.7	NA	7.3	12.9	Giantonio et al. 2007
	Aflibercept+FOLFIRI	≥2L	19.8	NA	6.9	13.5	Van Cutsem et al. 2012
	Ramucirumab+FOLFIRI	2L	13.4	NA	5.7	13.3	Tabernero et al. 2015
	Regorafenib	≥2L	1.0	NA	1.9	6.4	Grothey et al. 2013
	Trifluridine/Tipiracil	≥2L	1.6	NA	2.0	7.1	Mayer et al. 2015
Breast Cancer incl. Secretory Breast	Gemcitabine+Paclitaxel	≥2L	41.4	9.9	6.1 (TTP)	18.6	Albain et al. 2007
	Lapatinib+Capecitabine[c]	≥2L	22	9.9	5.5 (TTP)	17.0	Cameron et al. 2008; 2010
	Capecitabine+Docetaxel	≥2L	41.6	7.3	6.1 (TTP)	14.5	O'Shaugnessy et al. 2002
	Fulvestrant+Palbociclib	≥2L	24.6	9.3	9.5	NA	Cristofanilli et al. 2016
	Eribulin	≥2L	12.2	4.2	3.7	13.2	Cortes et al. 2011
Salivary Gland Cancer incl. MASC	Sunitinib	≥1L	0	NA	7.2 (TTP)	18.7	Chau et al. 2012
	Gefitinib	≥1L	0.0	NA	4.3/2.1	25.9/16.0	Jakob et al. 2015
	Platinum+Gemcitabine	≥1L	24.2	6.7	NA	13.8	Laurie et al. 2010
Soft Tissue Sarcoma	Eribulin[d]	≥2L	4.0	NA	2.6	13.5	Schöffski et al. 2016
	Sunitinib[e]	2L	6.8	NA	24.1	72.7	Demetri et al. 2006
	Regorafenib[f]	≥2L	4.5	NA	1.1-5.6	4.7-21.0	Mir et al. 2016
	Trabectedin	≥2L	9.9	6.5	4.2	12.4	Demetri et al. 2016
	Pazopanib[g]	≥2	4.0	9.7	4.6	12.6	van der Graf et al. 2012
	Dacarbazine+Gemcitabine	≥2L	12	10.2	4.2	16.8	García-del-Muro et al. 2011
	Olaratumab+Doxorubicin	≥1L[h]	18.2	8.3	6.6	26.5	Tap et al. 2016

NA, not available; NR, not reached.
[a] in patients with PD-L1 expression on at least 1% of tumour cells.
[b] for patients with RAS wt tumours.
[c] patients with HER2-positive advanced/metastatic BC.
[d] for patients with liposarcomas.
[e] patients with unresectable and/or metastatic gastrointestinal stromal tumours (GIST) after failure of imatinib.
[f] non-adipocytic STS (excluding liposarcomas).
[g] 59% of patients had at least one previous treatment.

ROS1-positive advanced NSCLC

Crizotinib (XALKORI, ALK, ROS1 and MET inhibitor) is the only ROS1 inhibitor authorised in EU for the treatment of adults with ROS1-positive advanced NSCLC. Crizotinib was approved based on the results from 53 patients with ROS1-positive NSCLC in the Phase I/II study PROFILE 1001. The objective response rate was 70% (95% CI: 56%, 82%). Median time to tumour response was 7.9 weeks. Median duration of response (DOR) had not been reached (95% CI: 15.2, NR), median PFS at the time of data cut-off was 19.3 months (95% CI: 14.8, NR), and median OS was not reached [probability of survival at

6 months 90.6% (95%CI: 78.8, 96.0), probability of survival at 12 months 79% (95% CI: 65.3, 87.8)]. No new safety signals were identified from patients with ROS1-positive NSCLC in Study 1001 as compared with the already established safety profile for crizotinib[30]. Updated results, for crizotinib in ROS1 rearranged advanced NSCLC, including overall survival, from PROFILE 1001, after a median follow-up of 62.6 months, showed consistent ORR 72%, with 6 CR (11%). Median duration of response is now reached, being 24.7 months (95%CI 15.2, 45.3). With 68% of PFS events (36/53 patients), median PFS was confirmed at 19.3 months (95%CI 15.2, 39.1). Median OS is now reached: death events in 26/53 patients [49%], median OS 51.4 months (95% CI, 29.3–not reached [NR]), probabilities of survival at 6, 12, 24, 36, and 48 months were 91%, 79%, 67%, 53%, and 51%, respectively. There was no apparent correlation between the specific ROS1 rearrangment and OS[31].

Efficacy data on crizotinib available in literature have been summarised by the Applicant in the table below:

Table 4: Efficacy and Safety of Crizotinib in Patients with ROS1-Positive NSCLC Across Published Studies

Study name	**PROFILE 1001[a]**	**AcSé[b]**	**OxOnc[c]**	**EUCROSS[d]**
Study type, location	**Phase I, United States**	**Phase II, France**	**Phase II, East Asia**	**Phase II, Europe**
No of Patients	50	37	127	29
Systemic Objective Response Rate (ORR) and Duration of Response (DOR)				
ORR, % (95% CI) By Investigator By BICR	 72 (58, 84) 66 (51, 79)[e]	 69 (52, 84) NA	 NA 72 (63, 79)	 69 (49, 84) NA
mDOR, months (95% CI) By Investigator By BICR	 17.6 (14.5, NR)* 18.3 (12.7, NR)	 NA NA	 NA 19.7 (14.1, NR)	 NA NA
Intracranial Objective Response Rate (IC-ORR) and Duration of CNS Response (IC-DOR) BICR				
Patients with CNS Disease at Baseline (n, as assessed by BICR) IC-ORR (%) (95% CI) IC-DOR BICR (months)	NA NA NA	NA NA NA	23 NA NA	NA NA NA
Progression-Free Survival (PFS)				

30 Xalkori EPAR EMEA/H/C/002489/II/0039.
31 Shaw AT et al. Crizotinib in ROS1-rearranged advanced NSCLC: updated results, including overall survival, from PROFILE 1001, Ann Oncol, July 2019; Volume 30, Issue 7: Pages 1121–1126.

median, months (95% CI) By Investigator By BICR With CNS disease at baseline Without CNS disease at baseline Patients remaining in follow-up for PFS, n (%)	19.2 (14.4, NR) NA NA NA 25 (50)	9.1 (5.4, NR) NA NA NA NA	NA 15.9 (12.9, 24.0) 10.2 (5.6, 13.1) 18.8 (13.1, NR) 45 (35)	NA NA NA NA NA
Safety				
Most common treatment-related AEs	Visual impairment (82%), diarrhea (44%), nausea (40%), peripheral edema (40%)	Edema, nausea, diarrhea, visual disorders (percentages not provided)	Elevated transaminases (55%), vision disorder (48%), nausea (41%), diarrhea (39%), vomiting (32%)	Visual disorders (48%), edema (41%), diarrhea (38%), bradycardia (32%)

[a] Shaw et al. 2014

[b] Moro-Sibilot et al. 2015

[c] Wu et al. 2018

[d] Michels et al. 2017

[e] Data for BICR reported in FDA benefit-risk summary for crizotinib in ROS1-postive NSCLC (Kazandjian et al. 2016) or Xalkori EU Assessment Report.

AE = adverse event; BICR = blinded independent central review; CI = confidence interval; CNS = central nervous system; NA = not available. NR = not reached; SAE = serious adverse event

*Shaw et al, Ann Oncol 2019 (updated results, median follow-up 62.6 months) (n=53 patients) ORR 72%, median DOR by inv 24.7 months (95%CI 15.2, 45.3); median PFS 19.3 months (95%CI 15.2, 39.1), median OS 51.4 months (95% CI, 29.3–NR).

According to ESMO guidelines, single-agent crizotinib is recommended in the 1L setting or as 2L in patients with stage IV NSCLC with ROS1 rearrangement. If patients have received crizotinib in the 1L setting, then they may be offered platinum-based chemotherapy therapy in the 2L setting.

The development of resistance to crizotinib represents a major hurdle and causes the vast majority of patients to eventually progress on therapy. Resistance can occur through: 1) "on target" mutations in crizotinib binding sites within the ROS1 tyrosine kinase domain, 2) "off target" mechanisms including activation of bypass signaling pathways (i.e., EGFR, RAS and KIT) and phenotypic changes such as epithelial to mesenchymal transition. The most commonly observed crizotinib resistance mutation has been ROS1-G2032R mutation in the solvent-front (i.e. solvent-exposed region of the kinase). Other mutations include solvent front D2033N, S1986Y/F, gatekeeper L2026M, and L1951R. Various drugs have been tested against these resistance mutations using *in vitro* studies[32][33].

Other ROS1 inhibitors are under evaluation in clinical trials, which include first generation ROS1 TKIs Ceritinib, Brigatinib and Cabozantinib, and second generation ROS1 TKIs Lorlatinib, Repotrectinib (TPX-0005) and DS-6051b[30].

32 Kartik Sehgal et al. Targeting ROS1 rearrangements in non-small cell lung cancer with crizotinib and other kinase inhibitors. Transl Cancer Res. 2018 August; 7(Suppl 7): S779–S786

33 Lin JJ, Shaw AT. Recent Advances in Targeting ROS1 in Lung Cancer. J Thorac Oncol. 2017 Nov; 12(11):1611-1625.

Intracranial activity of crizotinib: Information regarding any intracranial activity of crizotinib in ROS1-positive NSCLC patients with CNS disease are not available in literature. In PROFILE 1001 study, patients with brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease were allowed if appropriately treated and neurologically stable for at least 2 weeks (Xalkori *EPAR* EMEA/H/C/002489/II/0039). Publicly available reports of the study make no mention of CNS involvement at study entry, and no CNS endpoints are reported[3435].

Systemic response (inclusive, but not limited to CNS disease) and PFS have been reported in an Asian trial of crizotinib in ROS1-positive NSCLC, but intracranial activity was not specifically evaluated. In this trial, BICR assessed systemic ORR in patients with CNS disease at baseline was similar to that of patients without CNS disease (73.9% [95% CI: 51.6, 89.8] vs 71.2% [95% CI: 61.4, 79.6]). However, median PFS per BICR assessment was lower in patients with CNS disease at baseline compared with those without CNS disease at baseline (10.2 months [95% CI: 5.6, 13.1] vs. 18.8 months [95% CI: 13.1; NR]) (OxOnc)[36].

In ALK-positive NSCLC patients, crizotinib has shown numerically lower intracranial response rates (50% [95% CI: 28, 72] for measurable CNS disease) relative to systemic response (75.5% [95% CI: 67.8, 82.1] in the ITT population)[37]. Median duration of response for intracranial disease was 5.5 months (95% CI: 2.1, 17.3), compared to median duration of response with systemic disease of 11.1 months (95% CI: 7.9, 13.0). Crizotinib is a substrate of active efflux by the p-glycoprotein-1 (P-gp) transporter that is highly expressed within the blood-brain barrier (BBB)[38]. ALK positive patients treated with crizotinib were observed to have incidence of CNS progression of 41.4% at 12 months[39].

About the product

Entrectinib is an inhibitor of the tyrosine kinases TRKA, TRKB and TRKC (encoded by the genes NTRK1, NTRK2 and NTRK3, respectively), ROS proto-oncogene 1 receptor tyrosine kinase (encoded by the gene ROS1), and anaplastic lymphoma kinase (ALK; encoded by the gene ALK), with IC50 values for kinase inhibition in the low nanomolar range.

Gene rearrangements (fusions) in each of the genes encoding these target kinases have the potential to be oncogenic drivers, tend to be mutually exclusive, and have been observed at low incidence in a variety of tumour types.

The CHMP concluded that the following indications are approvable:

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older, with solid tumours that have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion,

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and

34 Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med. 2014;371:1963-1671.
35 Xalkori EPAR EMEA/H/C/002489/II/0039.
36 Wu YL, Yang JC, Kim DW, et al. Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2018;36:1405-1411.
37 Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK positive non-small-cell lung cancer. N Engl J Med. 2017;377:829-838.
38 Tang SC, Nguyen LN, Sparidans RW, et al. Increased oral availability and brain accumulation of the ALK inhibitor crizotinib by coadministration of the P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) inhibitor elacridar. Int J Cancer 2014;134:1484-1494.
39 Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2017;377:829-838.

- who have not received a prior *NTRK* inhibitor

- who have no satisfactory treatment options (see sections 4.4 and 5.1).

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.

Treatment with Rozlytrek should be initiated by a physician experienced in the use of anticancer medicinal products.

A validated assay is required for the selection of patients with *NTRK* gene fusion-positive solid tumours. *NTRK* gene fusion-positive status must be established prior to initiation of Rozlytrek therapy.

A validated assay is required for the selection of patients with *ROS1*-positive NSCLC. *ROS1*-positive status must be established prior to initiation of Rozlytrek therapy.

The recommended dose for adults is 600 mg entrectinib once daily.

The recommended dose for paediatric patients 12 years of age and older is 300 mg/m^2 body surface area (BSA) entrectinib once daily.

Table 5: Recommended dosing for paediatric patients

Body surface area (BSA)	Once daily dose
1.11-1.50 m^2	400 mg
≥ 1.51m^2	600 mg

It is recommended that patients are treated with Rozlytrek until disease progression or unacceptable toxicity.

If a planned dose of Rozlytrek is missed, patients can make up that dose unless the next dose is due within 12 hours. If vomiting occurs immediately after taking a dose of Rozlytrek, patients may repeat that dose.

Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment with Rozlytrek, in case of specified adverse reactions or based on the prescriber's assessment of the patient's safety or tolerability.

For adults, the dose of Rozlytrek may be reduced up to 2 times, based on tolerability. Rozlytrek treatment should be permanently discontinued if patients are unable to tolerate a dose of 200 mg once daily.

Table 6: Dose reduction schedule for adult patients

Dose reduction schedule	Dose level
Recommended dose	600 mg once daily
First dose reduction	400 mg once daily
Second dose reduction	200 mg once daily

For paediatric patients 12 years of age and older, the dose of Rozlytrek may be reduced up to 2 times, based on tolerability.

For some patients an intermittent dosing schedule is required to achieve the recommended reduced total weekly paediatric dose. Rozlytrek treatment should be permanently discontinued if patients are unable to tolerate the lowest reduced dose.

Table 7: Dose reduction schedule for paediatric patients

Action	**BSA of 1.11 to 1.50 m^2** (once/day)	**BSA ≥ 1.51m^2** (once/day)
Recommended dose	400 mg	600 mg
First dose reduction	300 mg	400 mg
Second dose reduction	200 mg, for 5 days each week*	200 mg
*5 days each week: Monday, Wednesday, Friday, Saturday, and Sunday		

Recommendations for Rozlytrek dose modifications for adult and paediatric patients in case of specific adverse reactions are provided in the below table.

Table 8: Recommended Rozlytrek dose modifications for adverse reactions in adult and paediatric patients

Adverse reaction	**Severity**	**Dosage modification**
Congestive heart failure	Symptomatic with middle to moderate activity or exertion, including where intervention is indicated (Grade 2 or 3)	• Withhold Rozlytrek until recovered to less than or equal to Grade 1 • Resume at reduced dose
	Severe with symptoms at rest, minimal activity, or exertion or where intervention is indicated (Grade 4)	• Withhold Rozlytrek until recovered to less than or equal to Grade 1 • Resume at reduced dose or discontinue as clinically appropriate
Cognitive disorders	Intolerable, but moderate changes interfering with activities of daily living (Intolerable Grade 2)	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline • Resume at same dose or reduced dose, as clinically needed
	Severe changes limiting activities of daily living (Grade 3)	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline • Resume at reduced dose
	Urgent intervention indicated for event (Grade 4)	• For prolonged, severe, or intolerable events, discontinue Rozlytrek as clinically appropriate
Hyperuricemia	Symptomatic or Grade 4	• Initiate urate-lowering medication • Withhold Rozlytrek until improvement of signs or symptoms • Resume Rozlytrek at same or reduced dose
QT interval prolongation	QTc 481 to 500 ms	• Withhold Rozlytrek until recovered to baseline • Resume treatment at same dose
	QTc greater than 500 ms	• Withhold Rozlytrek until QTc interval recovers to baseline • Resume at same dose if factors that cause QT prolongation are identified and corrected • Resume at reduced dose if other factors that cause QT prolongation are <u>not</u> identified
	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	• Permanently discontinue Rozlytrek
Transaminase elevations	Grade 3	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline • Resume at same dose if resolution occurs within 4 weeks • Permanently discontinue if adverse reaction does not resolve within 4 weeks • Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks
	Grade 4	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline • Resume at reduced dose if resolution occurs within 4 weeks • Permanently discontinue if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent Grade 4 events

	ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 2 times ULN (in the absence of cholestasis or hemolysis)	• Permanently discontinue Rozlytrek
Anaemia or neutropenia	Grade 3 or 4	• Withhold Rozlytrek until recovery to less than or equal to Grade 2 or to baseline • Resume at the same dose or reduced dose, as clinically needed
Other clinically relevant adverse reactions	Grade 3 or 4	• Withhold Rozlytrek until adverse reaction resolves or improves to recovery or improvement to Grade 1 or baseline • Resume at the same or reduced dose, if resolution occurs within 4 weeks • Consider permanent discontinuation if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent Grade 4 events
* Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0		

Type of Application and aspects on development

The CHMP did not agree to the Applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This decision was based on the following: "although the data in patients with NTRK fusion-positive locally advanced or metastatic solid tumours are promising, the quantification of the unmet need and the potential advantage of entrectinib over crizotinib in the ROS1-positive NSCLC patients is uncertain. As the applicant has not adequately substantiated that entrectinib is of major public health interest in ROS1-positive NSCLC patients, the CHMP was of the view that the request for accelerated assessment has not been satisfactorily justified".

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) 726/2004, based on the following criteria:

- The benefit-risk balance is positive.

The Applicant claims that, in the pooled analysis including 74 adult subjects, the ORR by BICR of 63.5% is clinically meaningful, and that responses were durable (median DOR of 12.9 months in responders). Responses were recorded in all solid tumor categories included in the integrated dataset independent of tumor histology or patients age, and similar response rates were demonstrated regardless whether patients had CNS disease at baseline or not. Intracranial activity was observed in patients with CNS metastases (IC-ORR 50%), with median IC-DOR of 8 months. For the 5 pediatric patients who had NTRK fusion and ≥6 months of follow-up, including 2 with primary CNS tumor, all patients achieved an objective response by BICR (2 CR and 3 PR). Based on safety data from 504 patients, the Applicant considered the safety profile favorable and entrectinib well tolerated. Most frequently reported AEs (in ≥25% of patients) were fatigue, constipation, dysgeusia, dizziness, diarrhea, nausea, anemia, peripheral edema, dyspnea, weight increased and blood creatinine increased. Grade 3-4 occurred in 60% of subjects. Most of grade 5 events (5%) occurred in the context of underlying malignancy or its complication and 2/24 were considered treatment related (sudden death and cardiac arrest). AEs could generally be well managed with dose reduction or interruption, and thus there was a low discontinuation rate due to AEs (9%). The safety profile of entrectinib in the paediatric population was considered consistent with the overall safety population except where noted.

- It is likely that the applicant will be able to provide comprehensive data.

The Applicant is proposing the following SOB measures:

"Specific Obligation number 1 (SOB-1) by 31 March 2027

In order to further confirm the histology-independent efficacy of entrectinib in adults and paediatric patients, the MAH should submit a pooled analysis of an increased number of NTRK fusion-positive patients from ongoing and proposed clinical trials."

Objectives: more precise characterisation of entrectinib efficacy across tumor types; more precise characterization of entrectinib lack of efficacy in a certain setting.

For SOB-1, the Applicant proposes to expande the pool with at least 200 additional patients with NTRK fusion positive solid tumors across histology. In this 200 patients, the Applicant will do every possible effort to enrol between 9-20 patients for the following common tumour types where NTRK fusions are rare: lung cancer, melanoma, colorectal cancer and non-secretory breast cancer; additional adult patients in all other indications, including primary CNS patients with responses assessed by RANO in this case; the Applicant commits to submit data on at least 3-5 pediatric patients ≥12 years (the vast majority of patients recruited so far in STARTRK-NG are below 12 years of age, numbers of ≥12 years are based on the current recruitment benchmark); the Applicant will also provide data on any additional pediatric patients <12 years in the ongoing STARTRK-NG and any potential new study (expected 22-27; 13 patients with less than 12 years already recruited since Dec 2017, of those 5 are in EU annex I, the Applicant will continue recruiting at least 15-20 children).

The timelines are based on the observed recruitment rate in STARTRK-2 (assuming 2.85 patients per month, it would take a minimum of 4 years to recuit 139 patients (indeed 61 efficacy evaluable patients have been recruited already) plus 12 months of follow-up and additional 12 months to analyse data and prepare full dossier) and taking into account competitive trials and new therapies.

An interim safety and efficacy analysis will be submit by the end of 2023 at the latest.

The following criteria will be used to assess and communicate the lack of efficacy for a specific setting in the expanding pool of NTRK fusion-positive patients. Once a new or currently under-represented tumour type has reached the stage of ≥ 13 patients in the pool that meet the integrated statistical analysis plan criteria, the applicant will timely inform assessors in case of lack of efficacy observed in this tumour type. Lack of efficacy would be defined as less than 4 responders in a group of sequentially enrolled 13 patients (i.e. ORR < 30%). 13 is the patient number derived from the STARTRK-2 study protocol, for an enrollment under a Simon 2-stage sequential testing design, which specifies a 13 patient first stage analysis before enrolling more patients into a second stage. If a new or currently underrepresented tumour type has not reached the stage of ≥ 13 patients in the pool that meet the integrated statistical analysis plan criteria, the applicant will continue the enrollment of patients with this tumour type until the SOB-1 deadline. The recruitment status wil be provided at the time of annual renewal. The Applicant also commits to share with EMA any additional efficacy analyses results that would have to be done upon request from any other health authority.

The Applicant will submit a safety report in all entrectinib-treated adolescent patients from STARTRK-NG (CO40778) and any other study with entrectinib where adolescent patients are enrolled. The report would include (but not limited to) assessment on growth and development and important risks such as bone fractures, neurocognitive disorders, CHF and QT interval prolongation. The safety report will be submitted by the end of 2023.

"Specific Obligation number 2 (SOB-2) by 31 March 2027

In order to further characterise entrectinib magnitude of efficacy across tumours based on biomarker status, the MAH should submit the results from tumor genomic profiling by plasma and/or tissue when

possible at baseline and progression together with clinical outcomes association per tumour histology for the patients in SOB-1"

Objective: more precise characterisation of entrectinib magnitude of efficacy across tumours based on biomarker status

The Applicant proposes to continue to collect plasma for circulating tumor DNA analysis and tumor tissue when medically feasible, and will use NGS to correlate the following with clinical outcomes: NTRK fusion status and partners, concurrent oncogenic driver mutations and concurrent additional alterations. Biomarker associations may not be statistically powered for correlation analyses given the rarity and diversity of biomarker alterations. Foundation Medicine F1 CDx for tissue samples and Foundation Medicine F1Liquid CDx for ctDNA (this platform will complete analytical validation studies in 2021, will be CE marked and anticipated to conform to IVDR in 2022. The Applicant will submit those analytical validation results as part of post-approval commitment and plasma samples will be used to identify genomic alterations at baseline and progression when medically feasible.

- Unmet medical needs will be addressed:

The Applicant considers entrectinib to fulfil unmet need based on:

- The high unmet medical need of patients with NTRK fusion-positive solid tumours, as entrectinib could be used to treat relapsed or refractory patients with these malignancies (i.e., for which there exists no satisfactory method of treatment) or who are unsuitable for existing treatment options (sensibility to excipients, CNS metastases).

- Data demonstrating entrectinib's potential to address this unmet medical need and bring a major therapeutic advantage to patients with NTRK fusion-positive tumours, irrespective of tumour type and inclusive of patients with CNS disease.

- Despite CMA approval for Vitrakvi for a similar indication, a possibility to approve a second product under CMA remains (EMA/CHMP/509951/2006, Rev.1) since uncertainty remains with regards to Vitrakvi's ability to fulfil the unmet medical need as more data are required to confirm efficacy, entrectinib can be approved under CMA as well.

The Applicant stated that Entrectinib is a weak substrate for the P-glycoprotein drug efflux transporter that regulates transport across the blood–brain barrier, and that a novel "Apical ER model" and *in-vivo* brain distribution models demonstrated unequivocally that entrectinib is a poor P-gp substrate with greater brain penetration.

Table 9: *In vitro* P-gp activity and brain penetration of entrectinib, crizotinib and larotrectinib

	In vitro P-gp activity (human)		*In vitro* P-gp activity (mouse)		CSF/Free plasma ratio[a]
	ER	AP-ER	ER	AP-ER	
Entrectinib	15	1.1	26	1.5	>0.2[b]
Crizotinib	28	3.5	29	4.9	0.03[c]
Larotrectinib	10	2.8	20	6.3	0.03[d]
Digoxin[e]	11	3.9	10	3.4	nd.

Cells in red, yellow and green indicate very strong, strong and weak/no P-gp interactions, respectively
a) Obtained after IV infusion up to 6 hours (h) of the tested molecule to rats
b) steady-state not reached after 6h
c) steady-state reached after 6h
d) steady-state reached after 5h
e) in vitro benchmark P-gp substrate
(AP-)ER, (apical) efflux ratio; CSF, cerebro-spinal fluid; nd, not determined; P-gp, P-glycoprotein

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

According to the Applicant, for adult and paediatric cancer patients whose solid tumours harbour oncogenic NTRK gene fusions, molecular therapy targeting the oncogenic proteins have demonstrated efficacy. The Applicant stated that entrectinib demonstrated strong clinical benefit in NTRK fusion-positive tumor and was well tolerated. Given the positive B/R of entrectinib, the current unmet need (especially for drugs targeting also CNS metastases) and the fact that comprehensive data will be available to confirm it, the Applicant believes that the benefits to public health of immediate availability outweigh the risks inherent in the fact that additional data are still required.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 100 mg and 200 mg of entrectinib as active substance.

Other ingredients are:

For the capsule content: tartaric acid, lactose anhydrous, hypromellose, crospovidone, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate;

For the capsule shell: hypromellose, titanium dioxide (E171), yellow iron oxide (E172, for yellow opaque capsule shell – 100 mg hard capsule), sunset yellow FCF (E110, for orange opaque capsule shell – 200 mg hard capsule);

Printing ink: shellac, propylene glycol, indigo carmine aluminium lake (E132).

The product is available in HDPE bottles with a child-resistant, tamper-evident closure and silica gel desiccant as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of entrectinib is *N*-{5-[(3,5-difluorophenyl)methyl]-1*H*-indazol-3-yl}-4-(4-methylpiperazin-1-yl)-2-[(oxan-4-yl)amino]benzamide corresponding to the molecular formula $C_{31}H_{34}F_2N_6O_2$. It has a relative molecular mass of 560.64 and the following structure:

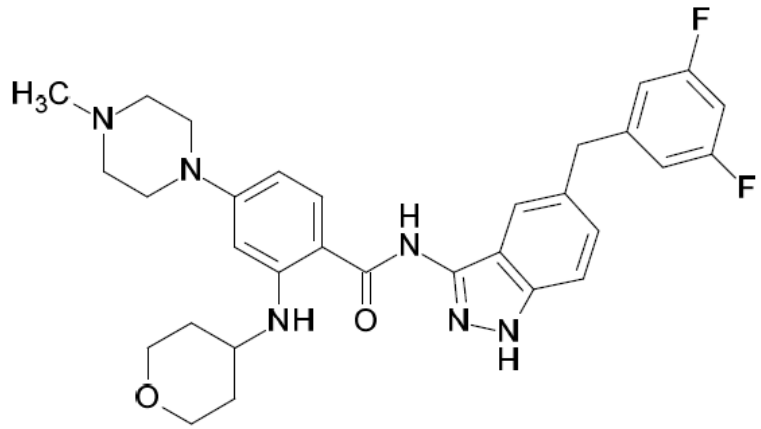


Figure 2: active substance structure

The chemical structure of entrectinib was elucidated by a combination of elemental analysis, infrared (IR) spectroscopy, ^{1}H nuclear magnetic resonance (NMR) spectroscopy, ^{13}C NMR spectroscopy, mass spectrometry and UV-Vis spectroscopy.

The active substance is a white to off-white or pale pink powder or powder with lumps. Entrectinib is non-hygroscopic as confirmed by DVS isotherm analysis. Entrectinib has a non-chiral molecular structure.

Entrectinib is poorly soluble in aqueous media, as the highest dose strength (200 mg) is not soluble in less than 250 mL water over the entire pH range of 1.2 to 6.8. Entrectinib is a free base and its solubility is strongly pH dependent: it exhibits higher solubility at lower pH relative to higher pH. The solubility of entrectinib in fed-state simulated intestinal fluid (FeSSIF) is substantially higher (approximately 40 times higher after 1 hour and 30 times higher after 24 hours) than in fasted-state simulated intestinal fluid (FaSSIF), which is indicative of a potential food effect. The pivotal clinical formulation (F2A) and the proposed commercial formulation (F06) include an acidulant (pH modifier), tartatic acid, in order to mitigate the effect of changes in gastric pH on clinical exposures.

Polymorphism

Polymorphism has been observed for entrectinib. Comprehensive screening for crystalline solid forms of entrectinib revealed multiple crystalline solid forms. From the discovered polymorphs, Form A was initially selected for further development. The relationship between these forms was established and described.

The solid-state properties of the active substance were measured by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), X-ray powder diffraction (XRPD), infrared (IR) spectroscopy, Raman spectroscopy, temperature-controlled X-ray powder diffraction (TCXRPD), and dynamic vapor sorption (DVS) analysis. Single-crystal X-ray structure analyses were performed on Form A, and Form C. In addition, an *in silico* crystal structure prediction (CSP) was performed to further assess the polymorphic landscape of entrectinib.

From the discovered crystalline solid forms, the solvent- and water-free crystalline Form A is the thermodynamically stable solid form at temperatures ≤-5 °C and Form C the stable one above 0 °C (enantiotropic relationship). *In silico* polymorph prediction confirmed the experimental finding that Form A and Form C are the most-stable polymorphs of entrectinib. Since the obtained energy difference between these two forms is within the error of calculation, the calculations do not allow to establish the thermodynamic relationship between Form A and Form C.

Form A was initially chosen for development and commercialisation. However, a series of unexpected manufacturing issues occurred with the final process step (Step 5-A) that prevented the isolation of the intended polymorph (Form A).

The Applicant decided to change the active substance polymorphic form for the product to Form C polymorph, and to modify the final manufacturing step from 5-A to 5-C.

Based on the extensive characterisation studies, a detailed assessment was conducted to demonstrate the comparability of entrectinib Form C with entrectinib Form A. It was demonstrated that Form C is comparable to Form A in terms of chemical and physical properties and stability. Forms A and C were further compared in a bioequivalence study (BE41049) and bioequivalence of Form A and Form C in the finished product was demonstrated.

Manufacture, characterisation and process controls

The active substance is synthesized in five main steps using two well-defined starting materials with acceptable specifications. Four chemical transformation steps (Step 1 – Step 4) are followed by crystallization, milling, and isolation (Step 5).

Due to unexpected issues with Step 5-A at the proposed commercial active substance manufacturer (manufacturer A), the Applicant decided to modify Step 5-A into Step 5-C and transfer it to a second manufacturer (manufacturer B). This alternative new Step 5-C has been developed specifically for the isolation of Form C, which has been duly characterised in terms of intramolecular bonding and crystal configuration. Steps from 1 to 4 are unchanged. Newly introduced materials for Step 5-C are supported with adequate specifications and analytical methods.

The Applicant intends to retain Step 5-A (Step implemented at manufacturer A that will no longer be used) in the dossier given that active substance Form A produced with this manufacturing process may be used for initial supply of the product in the EU. The proposal is to remove Step 5-A from the dossier and no longer use it for commercial supply, when all existing Form A active substance and finished product inventories have cleared from the Applicant's supply channels). Based on the demonstrated bioequivalence between finished products formulated with Form A and Form C and the physico-chemical comparability of the active substance of these two polymorphic forms, and the unmet medical need of the product, the CHMP has carefully considered and determined that this approach can be accepted. The traceability of the polymorphic form is assured as polymorphic form testing is part of the active substance specifications, linking this information with finished product batches under GMP requirements.

Critical process parameters (CPPs) for steps 1 – 5-A and step 5-C were identified. CPPs for step 5-C have been well defined in terms of input materials and process parameters; the relevant validation report confirms that the process is robust and capable to deliver Form C in a reproducible manner.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for starting materials, reagents and intermediate products (four intermediates are isolated), have been presented.

The starting materials and their observed impurities, reagents, solvents, process intermediates, and reasonably expected reaction by-products involved in the synthesis of entrectinib have been assessed for genotoxic risk. The assessment included *in silico* evaluation (using two complementary methods [DEREK for Windows and Leadscope Model] in accordance with ICH M7), Ames (bacterial reverse mutation assay) testing, chemical reasoning, and analytical testing.

Depending on the control strategy, compounds that were flagged positive *in silico* were subjected to further Ames testing, if necessary. If classified as known mutagens, carcinogens, or carcinogens with unknown mutagenic potential (Classes 1-3 in ICH M7), their entry point into the synthesis, as well as their fate and purge, were assessed further.

The experimental approach used analytical data to prove the absence of genotoxic/potential genotoxic impurities (GTIs) at low levels (analytical batch data), as well as deliberate addition of GTIs at higher levels in laboratory experiments and detecting their fate in the process ("spike and purge experiments"). An industry standard, five category weight-of-evidence classification scheme, as outlined in ICH M7, was used to classify the impurities on the basis of their mutagenic and carcinogenic potential.

A total of seven compounds were identified as genotoxic or potentially genotoxic, and control strategies for each have been developed.

Considering the indication for entrectinib (late-stage cancer), type of treatment (nongenotoxic anticancer agent), and expected longest duration of treatment based on patient life expectancy (less than 10 years), the use of less-than-lifetime (LTL) acceptable intakes for mutagenic impurities set out in ICH M7 is proposed for the control of Class 2 and Class 3 impurities. The same limits were also conservatively used to justify the control for the only identified Class 1 impurity. According to ICH M7 a maximum daily intake in the active substance of 10 µg/day for an individual genotoxic impurity and 30 µg/day for the sum of genotoxic impurities is allowed. Based on a dose of 600 mg/day of entrectinib, this corresponds to a limit of maximum 16 ppm for any individual genotoxic/potentially genotoxic impurity in the active substance.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

A single synthesis route (Steps 1-4) for entrectinib has been used during development. The route proved to be robust, and reliably delivered clinical supply of entrectinib. Eventually, the same route was developed into the final commercial manufacturing process.

The active substance is packed in a container which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance and colour (visual), identity (IR, HPLC, XRPD), water (Ph. Eur.), residual solvents (GC), residue on ignition (Ph. Eur.), palladium (ICP-MS), organic impurities (HPLC), assay (HPLC) and particle size distribution (laser diffraction).

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

Batch analysis data for 19 commercial scale batches from manufacturer A and 4 commercial scale batches from manufacturer B of the active substance have been provided. The results are within the specifications and consistent from batch to batch. Supportive batch analyses from numerous development scale batches have also been provided.

The active substance quality target product profile (QTPP) was determined through consideration of its use in the finished product, based on knowledge and understanding of its physical and chemical properties. The CQAs of the active substance were derived from the active substance quality target profile.

Stability

Stability data from four primary commercial scale batches of active substance Form A from manufacturer A stored in a container closure system representative of that intended for the market for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

Stability data from 3 primary commercial scale batches of active substance of the Form C from manufacturer B stored in a container closure system representative of that intended for the market for up to 6 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

Additional supportive stability batches of active substance of Form A (5 batches: 4 commercial and 1 pilot) and Form C (1 batch) from manufacturer A stored in a container closure system representative of that intended for the market for up to 12 months (Form C) and 36 months (Form A) under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, colour, water content, organic impurities, and assay (at every timepoint). Identity (physical form) by XRPD was tested after 6 months and then annually. Twelve-month data is presented for particle size distribution for primary stability batches (Form A).

Stability studies were performed using the analytical methods that are used for release testing. The methods used were validated and are stability indicating.

All tested parameters were within the specifications. No change in physical form was observed, regardless of the polymorph produced by the manufacturing process, under both long-term and accelerated conditions. This demonstrates that both intended entrectinib polymorphs (Form A and Form C) are stable in the solid state.

The stability data presented for entrectinib Form A are supportive of the stability of entrectinib Form C. In addition, the presented primary and supportive stability data for entrectinib Form C demonstrate the physical and chemical stability of this polymorph.

Photostability testing following the ICH guideline Q1B was performed on one commercial batch of active substance Form A and Form C. No changes on assay or organic impurities were observed.

In addition, stability of both entrectinib Form A and Form C was assessed in an open container study over 4 weeks at 100°C, the physical form was unchanged over this time. Solutions of entrectinib were prepared and heated to 40°C for 24 and 42 hours, - there was no change in purity or assay of entrectinib. Overall, the results demonstrate that entrectinib is very stable in the solid state and stable in solution at ambient temperature.

Results on stress conditions were also provided: acid, base, oxidative, thermal. Oxidative and hydrolytic degradation of entrectinib was assessed by exposure of entrectinib solutions to acid, base, and peroxide. Thermal stability in solution was assessed by heating solutions of entrectinib to 40 °C for 24 and 42 hours. Entrectinib remained stable under thermal (neutral pH) and acidic stress conditions. Entrectinib is unstable under very basic and oxidative conditions. However, the conditions under which degradation is observed are deemed not to be relevant for normal handling of the active substance.

Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is formulated as hard capsule in two strengths, containing either 100 mg or 200 mg of entrectinib as active substance.

Rozlytrek 100 mg hard capsule is a size 2 (18 mm in length), hard capsule with yellow opaque body and cap with ENT 100 imprinted in blue on the body.

Rozlytrek 200 mg hard capsule is a size 0 (21.7 mm in length), hard capsule with orange opaque body and cap with ENT 200 imprinted in blue on the body.

Different sizes, colour and imprint are considered sufficient to differentiate the strengths.

The two strengths are formulation proportional.

The proposed commercial formulation is an immediate-release hard capsule and is manufactured with standard excipients using conventional equipment and manufacturing processes.

The development of the entrectinib finished product includes elements of quality-by-design (QbD) and risk-based methodology. The quality target product profile (QTPP) has been used as the basis of design for the development of the finished product. The formulation was designed to achieve all of the attributes in the QTPP [immediate-release capsules for oral, 600 mg QD administration with or without food, in 2 dose strengths (100 mg and 200 mg), using entrectinib of polymorphic Form A or Form C as active substance with excipients compliant with Pharmacopoeial standards or respective standards for colourants/food additives, complying with product attributes for appearance, identity, content, uniformity of dosage units, dissolution, microbial limits, impurities, packaged in HDPE bottles with desiccant and child resistant closure, with a shelf life of minimum 24 months at or below 30 °C]. After definition of the commercial formulation, potential critical quality attributes (pCQAs) were identified for the proposed commercial formulation of the finished product, derived from the QTTP and prior knowledge.

Following a risk-based assessment, a subset of CQAs were identified as potentially being impacted by the manufacturing process variables and, therefore, were investigated in development studies.

Guided by an initial risk assessment, appropriate one-factor-at-a-time (OFAT) and multivariate studies were designed to evaluate the significance of process parameters and material attributes on the quality and performance of the capsule formulation.

A quality risk assessment (QRA) process was used to identify risks to the quality of entrectinib finished product, to identify the material attributes (MAs) and process parameters (PPs) that could have an impact on the relevant pCQAs. A risk ranking system for severity (low, medium or high risk) was used throughout the pharmaceutical process development. Process parameters and material attributes were identified as potential critical process parameters (pCPPs) and potential critical material attributes (pCMAs), if a small or large impact on any of the CQAs was expected. These were further investigated in small or pilot-scale experiments, in order to better understand the manufacturing process. After experimentation on commercial equipment and scale, the risk assessment was updated to the final QRA and target and proven acceptable ranges (PARs) were specified.

Entrectinib is a poorly soluble substance in aqueous media. As discussed earlier in the report, the pivotal clinical formulation (F2A) and the proposed commercial formulation (F06) include an acidulant (pH modifier), in order to mitigate the effect of changes in gastric pH on clinical exposures.

Polymorphic form A or form C are the intended active substance solid forms (Form A temporarily, until existing stock is depleted) and have been shown to be bioequivalent in the commercial formulation F06. The physicochemical properties of Form A and Form C active substance have been determined to be comparable.

Form A was the only form used in clinical studies conducted before initial commercial registration. The polymorphic form (pure Form A or pure Form C) is controlled by the active substance manufacturing process and the active substance specification.

As discussed under the active substance stability section, Form A and Form C have been shown to be stable during active substance storage (long-term, accelerated, and stress conditions in solid state).

The active substance solid-form integrity during finished product manufacture and on storage of the finished product has been appropriately discussed and the likelihood of any solid-state polymorph conversion of Form A or Form C into each other or into other solid forms during finished product manufacturing is deemed to be low.

The active substance particle size is controlled by a crystallization and milling process that produce material with a consistent particle size distribution in a specified range. The acceptance criteria are set on the final active substance to ensure material of appropriate quality for use in the entrectinib finished product manufacture. Milled and unmilled active substance were used in finished product (formulation F2A) to support RXDX-101-02 (STARTRK-2) registration-enabling Phase II study. Additionally, a bioavailability study (GP41341-Part 2) comparing F06 capsules manufactured using milled and unmilled Form A active substance was conducted. Average entrectinib plasma concentrations showed no apparent differences between entrectinib exposures from finished product manufactured using milled and unmilled active substance. The pharmacokinetic data indicates the absence of a correlation of *in vivo* exposure with active substance particle size within the ranges studied.

The processability of milled and unmilled active substance batches with varying particle size distributions was acceptable. Considering the controls established in the active substance specification, the particle size of entrectinib is not considered to have a significant influence on the finished product manufacturing process and critical quality attributes of entrectinib hard capsules, 100 mg and 200 mg.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or relevant standards for colourants/food additives. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Of note, acidulant tartaric acid has been included as an excipient. The rationale for its selection and inclusion in the formulation is discussed further in this section.

The 200 mg strength formulation contains the colouring agent sunset yellow FCF (E110) where azo dye component is present. The Applicant explained that the colouring agent sunset yellow FCF (E110) was selected to differentiate the two capsule strengths, to minimize the risk of dosing errors. The Applicant considers the 100 mg capsule strength to be the strength of choice for use in paediatric patients. This capsule strength does not contain the colouring agent sunset yellow FCF (E110), which is only present in the 200 mg F06 capsule strength. The Applicant has added a statement in 4.2 section of SmPC to clarify that "The 100 mg (size 2) capsules are recommended for paediatric patients". Another statement has been added in SmPC Chapter 4.4 Special Warnings and Precautions for Use, concerning the risk of allergic reactions of Sunset yellow FCF (E110).

The compatibility of entrectinib active substance with a number of excipients commonly used in solid oral formulations was evaluated. Binary mixtures of the active substance and excipients were prepared and evaluated in stability studies for any potential chemical and physical interaction. The excipient/active substance ratios were defined based on the excipient function and expected amount used in a typical formulation. The excipients evaluated did not exhibit significant incompatibility with entrectinib active substance.

Entrectinib has been formulated into several immediate-release capsule formulations for clinical use. Formulations F1 and F2A are the two clinical formulations used in safety/efficacy clinical studies (phase I and phase II) until clinical data (relative bioavailability) cut-off. Formulation F06 has been used in the relative bioavailability and bioequivalence studies and is the proposed commercial formulation.

The first generation of entrectinib finished product, formulation F1, developed was comprised of a dry blend of active substance free base and standard excipients. Since the solubility of the active

substance is strongly pH dependent, effects of food and proton pump inhibitors (PPI) on exposure were observed with this F1 formulation.

For this reason, another formulation F2A was developed, where an acidifying agent was introduced to provide an acidic environment for rapid drug dissolution, mitigate the food and PPI effects on exposure observed with the F1 formulation, and afford higher solubility irrespective of the pH of the local environment. Entrectinib F2A 200 mg capsule batches were used to support the RXDX-101-01 (STARTRK-1) Phase I study and RXDX-101-02 (STARTRK-2) registration-enabling Phase II study.

A third generation of entrectinib finished product, formulation F06, was developed as the proposed commercial formulation. In the commercial formulation, the acidifying agent used in formulation F2A was replaced with a more commonly used acidulant, tartaric acid, which was shown to be the most chemically compatible with entrectinib among all compendial acidulants investigated.

Capsule shells composed of HPMC were selected for the entrectinib F06 finished product, as they were considered more suitable than gelatin capsules for use within packaging containing a desiccant and the potential for incompatibility between tartaric acid and hard gelatin capsule (which can become brittle with a lower moisture content).

No *in vitro* comparison could be conducted among the three formulations used in the clinical setting since they have significantly different dissolution profiles. However, the RXDX-101-15 study demonstrated the bioequivalence of 200 mg F2A and F06 formulations. Additionally, a bioequivalence study was performed demonstrating equivalence of the finished product manufactured using Form A and Form C of entrectinib. The commercial manufacturing process for entrectinib finished product using either Form A or Form C active substance is identical.

The Applicant applied for a strength biowaiver for the formulation F06 100 mg strength. However, the use of T2EQ test initially used to decide upon similar dissolution profiles was considered not acceptable. The presented data showed differences in dissolution profiles between the two strengths, which had not been adequately discussed by the applicant. To be able to conclude whether the differences were active substance (solubility) rather than formulation related, the Applicant was asked to present comparative dissolution profiles at the same dose (i.e. two capsules of 100 mg versus one capsule of 200 mg). Two comparisons were carried out: with capsules containing Form A and Form C of the active substance (i.e. 2 x 100 mg vs 200 mg using entrectinib Form A and 2 x 100 mg vs 200 mg using entrectinib Form C).

The Applicant demonstrated that the variability in the dissolution is due to the formulation, specifically to the HPMC capsules, and it is not related to the solubility of the active substance.

In order to reduce the variability, the Applicant provided different studies and analysed the impact of different variables. However, the comparability of the profiles of the two strengths was demonstrated only when a sufficient number of units was tested, and when two 100 mg capsules (in a single sinker) against one 200 mg capsule were tested. This was considered acceptable.

In these conditions f2 bootstrapping demonstrated comparability in all relevant media tested (simulated gastric fluid sine pepsin (SGFsp) pH 1.2, sodium acetate pH 4.5, QC).

The comparison was successful with F06 (proposed commercial formulation) capsules containing Form A polymorph and F06 capsules containing Form C polymorph of the active substance.

The reason for accepting the biowaiver for 100 mg strength is also based on the comparison of dissolution profiles of the formulations tested *in vivo* (F2A and F06) and proved bioequivalent.

A range of method conditions was assessed in order to reduce the dissolution variability: apparatus, rotation speed, surfactant type and sinker type. None resulted in decreased variability of the dissolution at earlier time points. Similar variability was observed for the different types tested.

The dissolution profile data for various testing parameters and discriminating ability of the proposed dissolution method is acceptable as a quality control tool for batch release and stability testing of the 100 mg and 200 mg proposed finished product.

The primary packaging consists of HDPE bottles with a child-resistant, tamper-evident closure and silica gel desiccant. 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.

Manufacture of the product and process controls

The manufacture of entrectinib hard capsules involves conventional pharmaceutical technology and operational steps, such as blending, dry granulation, and encapsulation. The manufacturing process for the two dosage strengths, 100 mg and 200 mg, is identical. The two dosage strengths have the same qualitative composition and proportional fill weight.

The manufacturing process consists of several main steps: blending and screening steps, dry granulation, further blending, encapsulation and packaging. The process is considered a standard manufacturing process.

During manufacturing process development, potential critical process steps were evaluated. Process ranges and in-process controls are established to ensure a robust and reproducible manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on 3 consecutive commercial scale batches of each strength. 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.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, description of capsule content, identification (HPLC, UV), content (HPLC), degradation products (HPLC), uniformity of dosage units (weight variation, Ph. Eur.), water content (KF, Ph. Eur.), dissolution (HPLC) and microbial limits.

The proposed *in vitro* dissolution acceptance criterion is considered adequate to control the quality of both formulation strengths (100 mg and 200 mg) in the light of high variability observed up to the 45-minutes time point, which makes setting of a reliable and meaningful Q value at previous timepoints difficult.

In addition, the Applicant, declared that there is no added value in stronger discriminatory power since both acceptance criteria can discriminate bioequivalent against not bioequivalent tested profiles.

The justifications mentioned by the Applicant are supported also based on the following considerations.

Ph. Eur. chapter 5.17.1 ‘Recommendations on dissolution testing’ gives recommendations for setting Q value of conventional-release dosage forms at 75% but this chapter is non-mandatory. According to EMA/CHMP/CVMP/QWP/336031/2017 reflection paper the acceptance criterion Q value is usually set in the range between 75-85% and usually the time points are 15, 30 or 45 minutes, but other time points

may be used if justified. Indeed, if time points/Q values other than proposed in the decision tree would lead to discriminatory power, this is also acceptable.

In conclusion, on the basis of the Applicant' justification and provided data, although a specification of NLT 75% (Q) in 45 min would be preferable and more stringent, a single point specification with a Q value at a later timepoint could be considered adequate since no additional discriminatory power would be obtained using different acceptance criteria.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 commercial scale batches of each strength using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. Although palladium levels were well below the ICH Q3D threshold, control is retained on the active substance specification. The information on the control of elemental impurities is satisfactory.

During the review, upon request, the Applicant performed a risk evaluation regarding the presence of nitrosamines applying principles outlined in the notice "Information on nitrosamines for marketing authorization holders" (EMA Ref. EMA/189634/2019). No risk of presence of nitrosamines was identified for the product Rozlytrek 100 mg and 200 mg hard capsules.

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 and impurities testing has been presented.

Batch analysis results are provided for 100 mg capsules: 3 consecutive commercial scale batches using entrectinib Form C as active substance and 4 commercial scale and 2 pilot scale batches using entrectinib Form A as active substance; and for 200 mg capsules: 4 commercial scale batches using entrectinib Form C as active substance and 3 pilot scale batches using entrectinib Form A as active substance, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

For Rozlytrek 100 mg and 200 mg capsules containing entrectinib Form A, stability data on three primary commercial scale batches (per strength) of finished product stored for up to 24 months under long term conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging equivalent to that proposed for marketing. Further supportive data on three commercial scale batches (per strength) of finished product stored for up to 18 months under long term conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

For Rozlytrek 100 mg and 200 mg capsules containing entrectinib Form C, stability data on three primary commercial scale batches (per strength) of finished product stored for up to 3 months under long term conditions (30 ºC / 65% RH) and for up to 3 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to

those proposed for marketing and were packed in the primary packaging proposed for marketing. Further supportive data on a commercial scale batch (200 mg strength) of finished product stored for up to 12 months under long term conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

All primary stability batches are of the same composition as the intended commercial finished product, only the imprint on the capsule shell is different. Both the primary stability batches and the intended commercial batches are imprinted in blue with the same printing ink, however different imprints are used. This slight difference is not expected to have any influence on the stability behavior of the capsule.

Samples were tested for description of capsule and capsule content, assay, degradation products, water content, dissolution, and microbial limits. The analytical procedures used are the same as for release testing and are stability indicating.

Rozlytrek hard capsules were shown to be stable under all storage conditions evaluated, both in the primary stability program and supportive stability program. All samples met the acceptance criteria for the finished product.

A study was conducted on two commercial scale batches of entrectinib hard capsules 100 mg, and two commercial batches of entrectinib hard capsules 200 mg, containing the active substance of polymorphic Form A, in the proposed commercial primary packaging to evaluate the in-use stability of the finished product. The daily dose of three capsules were removed from the bottle and the bottle was left open for 3 minutes under 25°C/60% RH and 30°C/75% RH conditions. The procedure was repeated daily until approximately 20% of the original capsule fill count remained in the bottle. Analysis was performed on the remaining capsules. This procedure simulates how the product will be used by the patient. Per the procedure, the study had a duration of 35 days and 11 days for the 200 mg and 100 mg entrectinib hard capsules, respectively. The described in-use stability procedure was performed at the initial timepoint under 25°C/60% RH condition. No physical or chemical changes or microbiological contamination were observed during the in-use stability study. The storage conditions of the in-use study are 25°C/60% RH and 30°C/75% RH.

In line with the CHMP note for guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99), it is a recommendation of the CHMP for future quality development that the procedure is be repeated at the 24 months timepoint (end-of shelf-life) under 25°C/60% RH and 30°C/75% RH conditions and will be adapted to cover an in-use study duration (extended withdrawal period) of 42 and 90 days, respectively for the 100 mg and 200 mg formulation strengths, which correspond to the longest anticipated treatment durations with one bottle in line with the 2nd dose reduction schedules in the current label.

The available in–use stability data, in combination with the additional "open storage" stability data presented below, support the anticipated patient use of entrectinib hard capsules, 100 mg and 200 mg, without establishing a specific in-use shelf life.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one commercial scale batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed in any of the measured parameters (description, content per capsule of entrectinib, degradation products, water content, and dissolution), after direct exposure to ICH Q1B, Option 1 conditions, when compared to a dark control sample. It was demonstrated that entrectinib hard capsules, 100 mg and

200 mg, are not sensitive to light. This result is consistent with the absence of light sensitivity determined for the active substance.

An open storage stability study was conducted on one batch of entrectinib hard capsules 100 mg and 200 mg. The capsules were placed on stability (25°C/60% RH and 30°C/75% RH for 3 months) in their respective commercial container closure systems without the bottle cap. No discernible water uptake and no physical or chemical changes were observed during the open storage stability study.

Two commercial scale batches of each strength were tested in order to support the holding time of Rozlytrek bulk capsules prior to primary packaging. The capsules were stored in the intended bulk packaging for 12 months at 30°C /75% RH. Rozlytrek hard capsules were shown to be stable under the storage conditions evaluated.

Based on available stability data, the proposed shelf-life of 24 months and no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

The finished product containing either Form A or Form C is considered to have an equivalent stability based on the equivalent stability of the two polymorphs at the active substance level and the available stability data for the finished product manufactured with either entrectinib Form A or Form C.

Adventitious agents

The inactive ingredient lactose is derived from cow's milk. The milk is sourced from healthy animals in the same conditions as milk collected for human consumption. No other ruminant materials, with the exception of calf rennet, are used in the preparation of lactose. Lactose is produced in line with the criteria defined in the report EMEA/CPMP/BWP/337/02 "Risk and regulatory assessment of lactose andother products prepared using calf rennet".

Shellac derived from female lac bug is used as a component of printing ink. No concerns are raised regarding this excipient.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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.

The applicant has applied QbD principles in the development of the active substance and the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

The Applicant has provided a risk assessment regarding the potential presence of nitrosamines concluding that the risk of nitrosamine formation is considered negligible.

During the procedure the Applicant informed the CHMP that the proposed active substance manufacturer failed to reproduce the desired active substance Form A due to unexpected events and that the manufacturing site is not capable of further sourcing Form A. The Applicant has decided to change the active substance polymorphic form for the product and to use the Form C polymorph, and to modify the final manufacturing step of the active substance in order to assure that the desired polymorph is consistently produced. Substantial revision to Module 3 information has been done during the evaluation procedure and the revised documentation is acceptable. Based on the extensive characterisation studies, a detailed assessment was conducted to demonstrate the comparability of

entrectinib Form C with entrectinib Form A. It was demonstrated that Form C is comparable to Form A in terms of chemical and physical properties and stability. Forms A and C were further compared in a clinical bioequivalence study (BE41049) and bioequivalence of Form A and Form C in the finished product was demonstrated. The traceability of the polymorphic form is assured as polymorphic form testing is part of the active substance specifications, linking this information with finished product batches under GMP requirements. This approach was further accepted due to the unmet medical need for the product. When all existing Form A active substance and finished product inventories have cleared from the Applicant's supply channels, the Form A-related manufacturing steps are planned for removal from the registration dossier.

2.2.5. Conclusions on the chemical, pharmaceutical and biological 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.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

The Applicant should submit new in-use stability results according to the proposed specifications (including microbial limit testing and physicochemical degradation).

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic (PD) effects of entrectinib and its major metabolite M5 were assessed through characterisation in vitro of their anti-proliferative activity in cell lines expressing NTRK1, NTRK2, NTRK3, or ROS1 gene fusions compared to the ALK and ROS1 inhibitor Crizotinib. Additionally, entrectinib and M5 were tested for their ability to induce cell cycle arrest and apoptosis in fusion-positive cancer cell lines. In vivo, entrectinib alone compared to or in combination with the mitogen-activated protein kinase inhibitor, Trametinib, was tested for its effects on tumour growth inhibition (TGI) in mouse xenograft models representing various histologies and harboring TRKs or ROS1 fusions with various fusion partners. Moreover, entrectinib and M5 were also tested in mice intracranially injected with fusion-positive cancer cells to test their anti-tumor activity in the CNS.

2.3.2. Pharmacology

Mechanism of action

Entrectinib is an adenosine triphosphate (ATP) competitive inhibitor of receptor tyrosine kinases TRKA, TRKB, and TRKC, proto-oncogene tyrosine-protein kinase ROS, and anaplastic lymphoma kinase (ALK). Inhibition by entrectinib of the TRK, ROS1, and ALK kinase fusion activity, leads to inhibition of downstream signalling pathways, including phospholipase C gamma (PLCγ), mitogen activated protein kinase (MAPK), and phospho-inositol-3-kinase (PI3K)/protein kinase B (PI3K/AKT), which in turn leads to inhibition of cell proliferation, and induction of tumor cell apoptosis.

Genetic alterations in the form of fusion genes involving NTRK, ROS1 and ALK genes have known oncogenic and transforming potential. Fusion proteins may bypass the normal gene regulation which can lead to dominant over-expression and constitutive activation of the kinase domain and further resulting in activation of oncogenic downstream pathways and unconstrained cell proliferation. Such potentially oncogenic fusion genes appear in a multitude of tumour types with a variety of histologies and tissue origin. The Applicant suggests entrectinib can be used to inhibit such fusion gene driven oncogenic chain of events irrespective of tumour type in a histology-/tissue-independent ("agnostic") indication.

NTRK fusions have been described with over 20 gene fusion partners across a variety of tumour types including several paediatric tumours. Similarly, translocation of the kinase-encoding region of the ROS1 receptor tyrosine kinase has been found to rearrange with over 10 gene fusion partners in a variety of tumour settings. While ROS1 fusions are infrequently found in most indications, higher numbers (~2%) of NSCLCs harbouring ROS1 fusion genes have been described.

Primary pharmacodynamic studies

In vitro

The kinase inhibitory activity of entrectinib was determined in radiometric kinase assays. Entrectinib inhibited TRKA, TRKB, TRKC, ROS1, and ALK with IC_{50} values at low or sub nanomolar level (1.7, 0.1, 0.1, 0.2, and 1.6 nM, respectively). In addition, a major metabolite, M5, showed similar IC50 values (2.5, 0.1, 0.2, 0.2, and 1.9 nM, respectively). The target kinases could potentially all be inhibited at a clinical exposure level (Cmax= 3 720 nM, fu=0.22%, ~8 nM free); (M5: 30-50% of parent, fu=0.31%).

Binding selectivity of entrectinib was tested by a broad kinome screen comprising of a panel with a diverse set of 51 kinase assays containing representative members of serine-threonine and tyrosine kinase subfamilies. Biochemical characterization displayed that entrectinib is a strong and selective inhibitor of TRKA, TRKB, TRKC, ROS1, and ALK kinases with comparable IC50 values of 1.7, 0.1, 0.1, 0.2, and 1.6 nM, respectively. JAK2 and ACK1 showed a selectivity of <50 (however no evidence of JAK2 or ACK1 driven activity was obtained in the cell based anti-proliferation assay described below).

In a panel of 160 cell lines (154 cancer cell lines of different histological type and 6 non-tumor cell lines), which included 4 ALCL (lymphoma anaplastic large cell) lines and one NSCLC (non-small cell lung cancer) line bearing endogenous ALK gene traslocations, entrectinib exhibited a IC_{50} ranged between 0.020 to 0.081µM.

hHigh anti-proliferative activity was reported in 7 out of 154 cancer cell lines tested, of which 6 carried NTRK or ALK gene fusions (IC_{50} 0.47 – 81 nM). High anti-proliferative activity was also reported for one FLT3-ITD mutant cell line, MV-4-11. The latter activity described by the Applicant to be consistent with the high level of oncogenic addiction of this line to FLT3 and entrectinib exerting weakly inhibition of FLT3 (IC50=299 nM,150-fold selectivity to TRKA IC50=2 nM). Average IC50 of the remaining 157 cancer cell lines was 2.76 µM (range 0.017 – 6.05 µM). In another test (Report No. 1090429), high anti-proliferative activity was reported in 16 out of 303 cancer cell lines tested (which included 39 paediatric cancer cell lines), all harbouring NTRK, ALK or ROS1 gene fusions except that again anti-proliferative activity was also observed for the FLT3-ITD mutant cell line (IC50=431.3 nM). In this latter test M5 was also investigated and there was a high degree of correlation between the Entrectinib and M5 IC_{50} values across all cell lines tested (n=223 cell lines, Pearson r=0.7762, p<0.0001) as well as within lines with qIC50s <1 µM (n=20 cell lines, Pearson r=0.8946, p<0.0001). This was confirmed in a more detailed comparative cell viability study in the KM12 cell line (CRC, TPM3-NTRK1) where entrectinib and M5 showed equivalent potency in cell viability with IC_{50}s of 2.8 and 2.6 nM, respectively. These data suggest that the exposure of M5 may be relevant to the overall anti-tumor activity of entrectinib.

In vitro characterization of anti-proliferation activity of entrectinib and other ROS1 inhibitors in a human NSCLC cell line, CUTO-28, which contains the TPM3-ROS1 fusion gene compared to the ROS1 inhibitor crizotinib and another investigational ROS1 inhibitor, ceritinib in the Phase 2 clinical trials. The cellular IC50 (20.1 nM) of entrectinib in CUTO-28 cells is lower than crizotinib (36.6 nM) and Ceritinib (176.6 nM).

Entrectinib showed significant anti-tumor activity starting from 3 mg/kg in two human acute myeloid leukemia (AML) cell line (IMS-M2 and M0-91) xenografts driven by the ETV6-NTRK3 fusion gene (study 1087247). This effect was accompanied by inhibition of TRK signaling pathways and elimination of residual cancer cells from the bone marrow only in IMS-M2 tumor-bearing mice.

By using a panel of Ba/F3 cell lines transformed by NTRK1, NTRK2, or NTRK3 fusions with various fusion partners, the diversity of fusion genes tested for susceptibility to the entrectinib anti-proliferative effect was expanded. The use of NTRK-transformed cell lines was justified by the fact that cell lines naturally harboring NTRK fusion genes are rare, thereby limiting the diversity of TRK fusion proteins entrectinib could be tested against. Entrectinib inhibited the proliferation in all TRK-fusion driven cell lines tested, with IC50 values <6 nM, but not in the Ba/F3 parental line. Entrectinib also showed anti-proliferative activity in an engineered ROS1 fusion, ETV6-ROS1, transformed Ba/F3 line (Ba/F3-ETV6-ROS1)), with an IC50 of 5 nM.

Entrectinib completely inhibited phosphorylation of TRKA after treatment of NTRK1 fusion-dependent human CRC KM12 cells at concentrations of 10 nM and higher, with concomitant inhibition of phosphorylation of key downstream transducers. In addition, entrectinib treatment of ROS1 fusion-driven engineered Ba/F3 cells, induced a dose-dependent inhibition of ROS1 phosphorylation.

No in vitro data (e.g. binding or cellular potency) supporting the choice of species (rat and dog) for the non-clinical pivotal safety studies was provided.

In vivo

The in vivo potency of entrectinib was investigated in a panel of solid and hematological xenograft tumor models representing various histologies harbouring various TRK or ROS1 fusion genes (see Table 8). Overall, entrectinib treatment was studied in eight TRK-driven and three ROS1-driven tumor models, representing eight gene fusions and six tumor types (sarcoma, head and neck squamous cell carcinoma, NSCLC, CRC, glioma, and AML).

Table 8 Summary of Anti-Tumor Activity of Entrectinib in Xenograft Tumor Models

Model (Type)	**Gene Fusion**	**Tumor Response (%TGI) (at doses, mg/kg, PO, QD, or BID)**					
		0.3	**3**	**10**	**15**	**30**	**60**
KM12 (CRC)	*TPM3-NTRK1*	19% (QD)	64% (QD)	nd	>100% (QD)	>100% (QD)	nd
KM12 (CRC)	*TPM3-NTRK1*	nd	nd	nd	94% (BID)	93% (BID)	94% (BID)
KM12-Luciferase (CRC)	*TPM3-NTRK1*	nd	39% (QD)	101% (QD)	>100% (BID)	>100% (QD)	nd
CUTO-3 (NSCLC)	*MPRIP-NTRK1*	14% (QD)	>100% (QD)	>100% (QD)	nd	>100% (QD)	nd

Model (Type)	Gene Fusion	Tumor Response (%TGI) (at doses, mg/kg, PO, QD, or BID)					
		0.3	**3**	**10**	**15**	**30**	**60**
IMS-M2 (AML)	*ETV6-NTRK3*	nd	>100% (QD)	>100% (QD)	nd	>100% (QD)	nd
M0-91 (AML)	*ETV6-NTRK3*	nd	91% (QD)	>100% (QD)	nd	>100% (QD)	nd
CTG-0798 (Head and neck PDX)	*ETV6-NTRK3*	nd	nd	nd	>100% (BID)	nd	>100% (BID)
CTG-0798 (Head and neck PDX)	*ETV6-NTRK3*	nd	nd	nd	>100% (QD)	nd	nd
CRC PDX	*LMNA-NTRK1*	nd	nd	nd	>100% (QD)	nd	>100% (QD)
G002 (Sarcoma PDX)	*TPM3-NTRK1*	23% (QD)	84% (QD)	>100% (QD)	nd	>100% (QD)	nd
Ba/F3-ETV6-ROS1 (lymphoma)	*ETV6-ROS1*	nd	nd	nd	nd	nd	98% (BID)
LU-01-0414 (NSCLC PDX)	*SCD4-ROS1*	nd	70% (at 5 mg/kg BID)	nd	>100% (BID)	nd	>100% (at 45 mg/kg BID)
CTG-0848 (NSCLC PDX)	*CD74-ROS1*	nd	nd	nd	nd	>100% (BID)	>100% (BID)

%TGI=percent tumor growth inhibition; AML=acute myeloid leukemia; BID=twice a day; CRC=colorectal cancer; nd=not determined; NSCLC=non-small cell lung cancer; PDX=patient-derived xenograft; PO=by mouth; orally; QD=once a day.

A dose-range study was carried out in a TRK Fusion-Dependent KM12 (TPM3-NTRK1) CRC xenograft model resulting in calculated ED_{50} and ED_{90} values of 2.35 and 6.23 mg/kg, respectively (based on data through Day 20, entrectinib administration PO QD Day 7-20). QD dosing and BID dosing with half-doses (i.e. equal total dose) showed equivalent efficacy in the KM12-Luciferase (CRC, TPM3-NTRK1) xenograft tumour model. Dose-response was investigated in several of the PDX models with similar results, including ROS1-fusion-dependent models (see Table 8).

Anti-tumor efficacy was correlated with inhibition of downstream signalling pathway as investigated in sub-cutaneous KM12-Luciferase tumour-bearing mice. A dose-dependent suppression of p-PLCg1, pAKT, and pS6 was observed at doses of 5 mg/kg PO BID and above with maximal inhibition achieved at 15 mg/kg (tumours collected at 3, 8, and 12 hours after last (third) dose). Pathway suppression was maintained through 8 hours with recovery of signalling observed by 12 hours, particularly in the distal pS6 PD marker. These results were consistent with dose-ranging efficacy data in KM12 xenografts where doses < 1 mg/kg were ineffective and doses > 10 mg/kg resulted in maximal tumour efficacy. Pathway suppression in consistency with anti-tumor efficacy was also observed in the IMS-M2 AML (ETV6-NTRK3) tumour model. Along with a dose-dependent decrease in TRK phosphorylation (Y674/675) and total TRK protein, the phosphorylation of TRK downstream signalling molecules, PLCg, AKT and extracellular signal-regulated kinase 1/2 (ERK1/2), and signal transducer and activator of transcription 3 (STAT3) was

substantially reduced upon entrectinib treatment, with no observed alteration in corresponding total protein levels of PLCg, ERK1/2, and STAT3. Similar results were also obtained in the M0-91 AML (ETV6-NTRK3) model.

Anti-tumor effect at orthotopic sites was investigated in the IMS-M2 (ETV6-NTRK3) subcutaneous xenograft model, in which tumour cells spontaneously migrate to the bone marrow. After 3 weeks of treatment QD, no tumour- (i.e. human CD45-positive) cells could be detected in the bone marrow, whereas all vehicle-treated mice had a distinct tumor- (human CD45-positive) cell population.

Finally, the anti-tumor efficacy of entrectinib in intracranial tumour models was investigated in three intracranial brain orthotopic tumour models, the glioma models BNN2 and BNN4 (BCAN-NTRK1) and the CRC model KM12-Luciferase (TPM3-NTRK1) (see Table 9). Tumor growth inhibition, as analysed by MRI, and prolonged survival beyond treatment period ($p<0.0001$) were shown in BNN2 and BNN4 models treated with entrectinib, 50 mg/kg PO QD day 12-25. Entrectinib was also tested in a dose-ranging study using the intracranially-inoculated KM12-Luciferase tumour model. Therein, entrectinib demonstrated dose-dependent anti-tumour activity, as measured by luciferase-based bioluminescence, and prolonged animal survival throughout the course of the studywas shown in the KM12-Luciferase model. Full inhibition of increased bioluminescence was achieved only at 60 mg/kg BID, however all animals treated at doses above 15 mg/kg BID or 30 mg/kg QD survived through the 28-day treatment period (vehicle group succumbed due to tumours by day 16).

Table 9 Summary of Anti-Tumor Activity of Entrectinib in Intracranial Tumor Models

Model (Type) [Study No.]	**Gene Fusion**	**Dose**	**% Survival (Animals Survived/ Group Total)**
BNN2 (Glioma) [Cook et al. 2017]	*BCAN1-NTRK1*	• Vehicle • 50 mg/kg QD	• 0% (0/9)[a] • 100% (9/9)
BNN4 (Glioma) [Cook et al. 2017]	*BCAN1-NTRK1*	• Vehicle • 50 mg/kg QD	• 0% (0/9)[a] • 100% (9/9)
KM12-Luciferase (CRC)	*TPM3-NTRK1*	• Vehicle • 60 mg/kg BID	• 0% (0/9)[b] • 100% (9/9)
KM12-Luciferase (CRC) [Fisher et al. 2020]	*TPM3-NTRK1*	• Vehicle • 1 mg/kg BID • 5 mg/kg BID • 10 mg/kg QD • 15 mg/kg BID • 30 mg/kg QD • 60 mg/kg BID	• 0% (0/9)[c] • 0% (0/9) • 11% (1/9) • 67% (6/9) • 100% (9/9) • 100% (9/9) • 100% (9/9)

BID=twice a day; CRC=colorectal cancer; QD=once a day.

[a] Survival on Day 25.

[b] Survival on Day 14.

[c] Survival on Day 28.

Secondary pharmacodynamic studies

Entrectinib was screened across a panel of 293 diverse set of protein kinases, including serine-threonine subfamilies (in addition to the kinome screen reported in the primary pharmacodynamic *in vitro* section). Entrectinib at 100 nM inhibited 6 kinases >95% (ALK, ROS1, TXK, TRKA, TRKB, and TRKC), 2 kinases >80% (CSF1R and JAK2), 4 kinases >60% (ITK, LTK, MuSK, and TYK2), and 18 kinases >40%. The remaining 256 kinases showed minimal inhibition.

In vitro screening assays investigated secondary pharmacodynamics effects of a single concentration (10 µM) of entrectinib and its major metabolite M5 on ligand binding to 89 targets (receptors, ion channels, and transporters. The results of these assays showed significant binding (≥50%) at concentrations far exceeding the highest clinical entrectinib and M5 plasma concentration (free Cmax,ss=~0.007 µM; free Cmax=~0.004 µM, respectively) by ~1400- and 2500-fold, respectively, against several targets (α1A, 2A, 2C; CB2; D1, D2S, D3, D5; δ (DOP); GR; sigma2; OX; H1; H2; kappa; M1, 4, 5; µ [MOP], PPARγ, 5-HT1B, 2A, 2B, 5a, 6, 7; sst4, COX2; L-type Ca2+ channels [dihydropyridine, verapamil, diltiazem, phenylalkylamine, and benzothiazepine sites], potassium channel hERG and sodium channel (site 2); norepinephrine, serotonin, dopamine, 5-HT, and choline transporters).

Safety pharmacology programme

Entrectinib has been investigated for potential effects on CNS, cardiovascular and respiratory systems in a battery of mostly GLP compliant *in vivo* and *in vitro* studies.

The CNS/neurobehavioral safety profile was investigated in the rat, by a modified Irwin screen carried out in female rats day 1 and day 14 after entrectinib treatment (0, 50, 100, 200 mg/kg/day PO, 14 days or single dose). At 200 mg/kg/day, no effect on Day 1, slight to moderate incoordination from Day 7 and abnormal gait on Day 14 were observed. A NOEL of 100 mg/kg/day (Day 42 AUC_{0-24}=111±37.1 and C_{max}=6.44±2.3) results in ~2-fold margin to recommended human dose. In addition, a neurobehavioral exploratory study was carried out in dog. In the 7-day repeat dose study (0, 80, 120 mg/kg/day, PO, QD) no CNS signs were seen at 80 mg/kg (highest AUC_{0-24} 73.9 µM·h Day 7) resulting in a 1.3-fold margin to clinical exposure.

In the hERG assay, entrectinib was evaluated in stably transfected HEK293 cells at 0.05, 0.5, 1.5, 15 µM, resulting in concentration-dependent inhibition, ranging from 16% to 90% at tested concentrations and an IC50=0.6 µM (~75-fold the clinically relevant unbound fraction in plasma). Metabolite M5 was evaluated on hERG expressed in mammalian cells at 0.3, 1, 3, 10 µM, resulting in concentration-dependent inhibition, ranging from 0% to 50% at tested concentrations and an IC50=10.4 µM, which is >2000 fold the clinically relevant unbound fraction in plasma (according to the Applicant, solubility limitations may have led to underestimation of the hERG inhibition).

A cardiovascular (CV) GLP study was carried out in telemetered dogs (2/sex), with escalating doses PO at 0, 60, and 120 mg/kg (with 1-week washout), CV parameters reported from 60 minutes before to 7 hours after treatment. No effects were observed on systemic arterial pressure, heart rate, ECG intervals (including QT and QTc), or body temperature at any of the doses tested; thus, the NOEL for cardiovascular parameters and body temperature was 120 mg/kg, with C_{max} estimated to range from 3.1 to 7.0 µM (based on the Day 1 exposure data from the 4-week repeat-dose toxicity study) resulting in ~2-4 fold exposure margins above clinical C_{max}. A non-GLP CV study was carried out in 3 conscious telemetered female dogs, receiving a single oral administration of vehicle or 300 mg/kg

entrectinib, 7 days apart. A slight transient increase in blood pressure from 30 minutes to 1 hour post dose was recorded. Body temperature increased 0.5 ^{o}C up to 2.5 hours post treatment. No notable changes in CV parameters in comparison to control, resulting in a NOEL at 300 mg/kg. In addition, an exploratory repeat-dose study in dog was carried out on female dogs (4/group), administrated PO QD at 80 or 120 mg/kg for 7 days followed by an 11-day recovery. Moderate increases in QT and QTcF intervals were noted, in 1 animal, in the recovery phase, day 8 and 9 at 120 mg/kg (C_{max} 7.08 mM, AUC_{0-24}=144 µM·h, ~2-fold clinical C_{max}).

The respiratory effects of entrectinib was investigated in female rats, given a single oral dose of 0, 50, 100, or 200 mg/kg. Respiratory parameters including tidal volume, minute volume, respiratory rate, peak inspiratory flow, peak expiratory flow, inspiration time, expiration time, relaxation time, and Penh (an index of bronchoconstriction) parameters were collected using whole body plethysmography. No relevant effects were observed at any of the doses administered; the NOEL for respiratory function was 200 mg/kg.

Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies were performed with entrectinib.

2.3.3. Pharmacokinetics

Absorption, distribution, metabolism, and excretion (ADME) studies for entrectinib have been conducted in mice, rats, and dogs. The studies were carried out primarily with oral administration, which is the proposed clinical route of administration. Pharmacokinetic analysis following repeated doses was performed in pharmacology studies in mice and in all repeated-dose toxicology studies.

In all GLP studies [Analytical Methods and Validation Reports: 1087313, 1087318, 1087319, 1087320, 1087321] rat and dogs plasma concentrations of entrectinib and M5 were measured using a validated LC-MS/MS-based bioanalytical method. The LC-MS/MS methods used in non-GLP nonclinical studies were either validated or qualified. Validation work was performed according to either the Organization for Economic Co-operation and Development (OECD) GLP principles or US Code of Federal Regulations (CFR) 21 part 58 and/or in adherence to standard operating procedures (SOPs). The validated assays were considered reliable as no significant deviations from GLP principles or SOPs were reported that could have a potential impact on the reliability of the validation and resulting PK/TK analysis. The fact that the validation of the assays was not conducted under a formal claim of GLP is considered to have no adverse impact on the quality of the validation of the methods, and hence on the resulting PK/TK analysis. Non-validated LC-MS/MS methods were also developed and used for the analysis of plasma and brain samples for preliminary or exploratory PK studies in mice, rats, and dogs. In addition, radioactivity levels were measured in blood, plasma, urine, and fecal samples from mass balance studies in rats and dogs. For all validated methods the quantification range, and the intra- and inter-assay accuracy and precision (within ±15% and ≤15% coefficient of variation [CV], respectively, and ± 20% and ≤20% CV at lower limit of quantification [LLOQ], respectively) are presented in the table below.

Table 10: Summary of bioanalytical validation studies for rat and dog plasma

Species	Analyte	Intra-assay		Inter-assay		Study No. [Report No.]	Study No. in which BA Method Implemented [Report No.]
		Accuracy % bias	Precision % CV	Accuracy % bias	Precision % CV		
Rat	Entrectinib	1.0 to 8.0	≤15.5			[1087321][a]	[1087346][a]
	Entrectinib	–14.5 to 3.5	≤8.8	–9.1 to –0.9	≤6.5	[1087313][b]	[1087349][c], [1087360][d], [1087361][e]
	M5	–9.0 to 0.5	≤9.9	–7.3 to –1.7	≤7.3		
	Entrectinib	–6.80 to 4.67	≤6.43	–4.67 to 2.67	≤4.81	[1087320][f]	[1087353][g], [1087348][c]
	M5	–6.93 to 7.67	≤5.68	–3.87 to 2.67	≤4.42		
Dog	Entrectinib	0.8 to 14.3	≤17.4	6.0 to 9.4	≤9.7	[1087319][a]	[1087335][a]
	Entrectinib	–13.0 to 2.80	≤7.31	–7.00 to 0.267	≤7.24	[1087318][f]	[1087343][c], [1087342][d]
	M5	–12.3 to –2.00	≤5.18	–8.67 to –5.60	≤5.00		

CV=coefficient of variation.
Range: 10–10,000 ng/mL.
[a] Study performed by Accelera S.r.l., Nerviano (MI), Italy.
[b] Study performed by Ignyta, Inc., San Diego, CA, USA.
[c] Study performed by Covance Laboratories, Inc., Madison, WI, USA.
[d] Study performed by Charles River Laboratories, Inc., Horsham, PA, USA.
[e] Study performed by Charles River Laboratories Ashland, LLC, Ashland, OH, USA.
[f] Study performed by InVentiv Health Clinical Lab, Inc., Princeton, NJ (currently Syneos Health, Princeton, NJ, USA).
[g] Study performed by BioReliance Corporation, Rockville, MD, USA.

Absorption

In vitro

In vitro absorption study on the assessment of the bidirectional permeability in the Caco-2 cell monolayer model showed that entrectnib at 0.1(μM) presented an apparent permeability coefficient (P_{app}) of 0.838 (10^{-6} cm/s) in the absence (-) of the transporter inhibitor cyclosporine A (CsA) and of 1.07 10^{-6} cm/s in the presence (+) of CsA, values that were lower than the reference compound minoxidil [(-) 5.67 and (+) 5.25 (10^{-6} cm/s)] but higher than the second reference compound atenolol [(-) 0.244 and (+) 0.191 (10^{-6} cm/s)]. Additionally Entrectinib exhibited an efflux ratio of 4.22 in the absence of the CsA, which was reduced to 0.808 in the presence of cyclosporine. Entrectinib with its moderate permeability may be considered a substrate of an apical efflux transporter such as P-glycoprotein.

In vivo absorption studies Entrectinib after single oral dose (10mg/kg), the intended route of administration in patients, was readily adsorbed with a low/moderate plasma clearance and large volume of distribution with a bioavailability of 76% in mice and 33% in rats. Plasma levels declined with a terminal half-life of 2.94 – 3.82 hours respectively. In male dogs (10mg/kg) the maximum concentration has been reached approximately 2h post-dose in both plasma and blood with a mean blood-to-plasma radioactivity ratio of Cmax and AUC∞ approximately of 4 and 2.7 respectively, suggesting a preferential distribution into the blood. Oral bioavailability in dogs was 74.4% while plasma level decreased after 4.0 after administration. Major metabolite M5 constituted 27.0% (oral) or 4.54% (IV) of the total circulating radioactivity in plasma in dogs and approximately 0.7 to 0.9% (oral) or 0.6 to 0.8% (intravenous) in male e female rats. Entrectinib and M5 pharmacokinetics data extrapolated from *in vivo* study on KM12-Luciferase (TPM3-NTRK1) intracranial/subcutaneous tumours mice models at doses repeated demonstrates a good dose-dependent PK/PD/efficacy relationship. Exposure in terms of Cmax and AUC(0-24h) increasing dose approximately over the 5 to 60 mg/kg BID on both evaluation days (1 and 8) and at > 3 mg/kg/day in the intracranial and subcutaneous model respectively. On the other hand the exposure (AUC(0-24h)) to M5 was found to be 8–15% on both Day 1 and 8 and approximately 9% to 16% on all occasions, of that of entrectinib exposure in the intracranial and subcutaneous model respectively. No marked accumulation in plasma exposure was observed neither in subcutaneous or in the intracranial model on Day 8 of QD or BID dosing as resulted from respective accumulation ratios for AUC(0-24) that ranged from 0.51 to 0.95 and 0.62 to 1.1 in the intracranial and from 0.65 to 1.4 and 0.87 to 1.4 in the subcutaneous model for entrectinib and M5 respectively.

Distribution

Entrectinib was extensively bound to plasma proteins in mouse, rat, dog, monkey including human, with high fractions bound >99% across all species. In human blood *in vitro* study, entrectinib and M5 at 3 μM showed blood-to-plasma ratios of 1.3 and 1.0, respectively with a fraction bound >99%.

Radio-labeled entrectinib resulted widely distributed into tissues with mean Cmax occurring at either 3 or 8 hours postdose, to decline after this time but with moderate levels of radioactivity, 168 hours postdose, still detectable in tissues like gland tissues. Excluding bile and urine, the highest mean Cmax levels were observed in liver, lungs, adrenal glands, kidneys, renal cortex, and thyroid while the lowest mean Cmax values included bone, testes, eyes, seminal vesicles, and epididymis.

Brain-to-plasma AUC ratios were 0.219 and 0.315, respectively for entrectinib and M5 after single oral dose of entrectinib 20mg/kg in male rats. Additionally, higher brain levels were observed following achievements of steady-state conditions by either repeated oral doses or constant infusion confirming brain penetration of entrectinib in mice, rats and dogs with brain-to-plasma concentration ratios of ~0.4 in mice, 0.6–2.5 in rats, and 1.4–2.2 in dogs at 24 hours post last oral dose.

Following entrectinib 6mg/kg single IV dose, instead, male rats showed a brain/plasma ratio of 0.6 at 6h post start of infusion (SOI) with a plasma and brain concentration at the same time equal to 1.4 and 0.84 μM respectively. A further confirmation that entrectinib penetrates the BBB and is retained in the brain, is given by anti-tumor activity observed in tumours residing in the brain. Summary of pharmacodynamics, pharmacokinetics and efficacy data observed with entrectinib treatment in the KM12-Luc intracranial tumour mouse model showed that oral dose of 5 mg/kg induced a tumour inhibition of 82.1 % between 3-12 hours post dosing and an AUC0-24h of 12.3 μM·hr.

No studies on placental passage or excretion into milk was carried out.

Metabolism

In vitro studies performed in rat, monkey, dog, human and mouse hepatocytes, at concentration of 10 μM, entrectinib represented the major component with approximatively moderate turnover of 44%, 45%, 46%, 68%, 70% respectively. Concerning to the drug related materials formation in the studied species, M14 was most represented in rats 19%, M7 in dogs and humans with 36% and 12% respectively while M5 in monkeys with 16%. Incubation of [14C]entrectinib with monkey, dog, human, rat, and mouse liver microsomes revealed [14C]entrectinib presence approximately from 33% to 79% respectively together with major radioactive peaks attributed to M5 detected in monkeys 40.4%, in dogs 29.9% and in human 28.4%. M7 were detected in all species, prevalently in dogs 36.5%, while M1, M3 and M13 were observed in monkey 5.05%, 5.40%, 10.6% and human 7.48%, 1.97%, 5.74% liver microsomes respectively. Metabolite M2 was only detected in human liver microsomes 8.05%. M11, the major circulating components detected in human plasma (18.6%) together with M5 (12%) between 0-24 hours, was only observed in human hepatocytes (3%) and in the recombinant human UGT isoform 1A4 (3.94%). In human hepatocytes oxidative metabolism of entrectinib resulted mainly in N-demethylation at the piperazine (M5) 12%, oxidation at the benzylic position (M2) 5.5%, and combinations thereof (M1 1.8%, M3 0.5%). The formation of an N-oxide at the piperazine (M7) was observed to some extent 3.5%. Individually, the M5 (N-demethylation) was the most abundant metabolite, accounting for 12% (representing 41% of entrectinib metabolism) and M11 5.5% of drug related material after 120 minutes. Therefore glucuronide conjugation represented 19% of entrectinib metabolism in human hepatocytes. Clearance values of both Entrectinib and M5 showed concentration-dependent elimination in the selected time frame of 4 days and were estimated to be 20 and 9.3 μL/min/mg at the corresponding initial concentrations of 0.1 μM, 17 and 8.7 μL/min/mg at 1 μM, and 5.8 and 3.9 μL/min/mg at 10 μM, respectively in cell culture medium of long-term hepatocyte fibroblasts co-cultures from human. The major CYP450 isoforms involved in the metabolism of entrectinib were CYP3A4 (56%), CYP2C19 (79%),CYP2C9 (85%), CYP2C8 (86%) and CYP1A1 (90%) following incubation of entrectinib 10 μM with, 20 pmol/ml of recombinant cDNA

expressed enzymes CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, 40pmol/ml of CYP2C18, CYP2E1 and 0.8 mg/ml of Human Liver Microsomes (HLM), for 1 hour. After this period the CLintr in HLM system was about 0.26 µL/min/mg protein and the percentage remaining 73%. Single oral dose in rats showed that M12 was the major metabolite in plasma with 90% in males and 46.3% in females to then decrease in both gender after 4 hours post dosage compared to entrectinib detected to 94%. Following IV dosing, entrectinib remained the predominant component in rat plasma 100% while M12 has not been detected. The difference of M12 formation between IV and oral dosing indicates that M12 is most likely formed in the intestine. In rat faeces, after 24-48 hours post PO dosing the parent remained the predominant component >70% in both sexes while after 24-48 hours post IV dosing, M5 was the major metabolite, with 71.1% and 62.9% in male and female respectively. In male dogs plasma and faeces after 2 hours post single [14C]entrectinib, 10 mg/kg oral or 1 mg/kg IV dose, entrectinib was the major circulating component: 61.9% or 87.9% respectively. M5 was the major metabolite in circulation after oral dosing and exceed with 70% the parent at 6 hours postdose. After IV dosing, M7, accounted for approximately 27% of radioactivity in plasma collected at 5 minutes.

Excretion

In rats, faecal excretion, proved to be the predominant route of elimination form from both male 97.4%-102% and female 97.7%-99.5% while urinary excretion represented less than 1% and 2% after single oral and IV dosing respectively. The majority of the radioactivity was eliminated through faeces within 48 hours post dose.

The total mean recovery in male dogs, as extrapolated from studies report 1087301 and 1087297 was 85.8% and 79.1% through 120 hours postdose after oral and IV administration, respectively. The majority of the radioactivity was however eliminated within 48 hours post-dose after oral and 72 hours after IV dosing. Faecal excretion was the predominant route of elimination from male dogs after 10 mg/Kg oral (84.6%) or 1 mg/kg IV dose (78.0%) of [^{14}C]entrectinib. Urinary excretion represented a mean of 0.401% and 0.612% of the administered radioactivity after oral or IV dosing, respectively. In conclusion faecal excretion was the predominant elimination route for dogs and rats. No data was provided about mice excretion.

Table 11: Excretion patterns in rats and dogs following a single dose of [^{14}C]entrectinib

Species	Route	Dose (mg/kg)	Sex	Recovery of Dose (%)			
				Urine	Feces	Other[a]	Total
Rat	IV	2	Male	1.64	102	1.21	105
			Female	1.28	99.5	1.32	102
	PO	20	Male	0.849	97.4	0.570	98.8
			Female	0.686	97.7	0.674	99.0
Dog	IV	1	Male	0.612	78.0	0.546	79.1
	PO	10		0.401	84.6	0.750	85.8

Pharmacokinetic drug interactions

No non-clinical pharmacodynamic drug interaction studies were performed with entrectinib.

Other pharmacokinetic studies

Entrectinib is a poorly water-soluble free base that exhibits polymorphism and can potentially exist in multiple solid forms. In a crossover study male Beagle dogs were treated orally with 60 mg/kg dose (dose volume 5 mL/kg)of two polymorphic forms of Entrectinib, Lot/Batch Number N0900202 (Form 1) and TIF19421/40E (Form 2). As declared by the Applicant, terminology was changed during development and Form 2 corresponded to Form A that is the only form used in clinical studies

conducted before initial commercial registration. The applicant clarified that Form I corresponds to Form B and was only used in the toxicology studies in rats (4 week intermittent, study 1087348) and dogs (4 week intermittent, study 1087335). Form II corresponds to Form A, form to be used in clinical studies and selected for commercial manufacturing based on better chemical profile

Differences in the 2 polymorphic forms I (B) and II (A) used do not affect the assessment of the toxicological studies since, no significant differences in Cmax and AUC, as well as in tmax and t1/2, emerged in PK study 1087279 where dogs were treated orally (single dose of 60 mg/kg) with the two entrectinib polymorphic forms in solution, with a one-week washout between the two treatments. The biocomparability of the 2 solid Forms is only valid for the dog species in which a direct comparison was performed. However, considering that the majority of toxicology studies, including the pivotal 13-week rat and dog studies, tested the Form II (A) also used in clinical trials, results from toxicology studies are considered reliable for extrapolation to humans. Similar plasma exposures to Entrectinib were observed in dogs when orally administrated in suspension (intended formulation used in toxicity studies) or solution to male Beagle dogs at a single dose of 30 mg/kg with two lots of Entrectinib of 2nd and 3rd generation: CA14-0258 and CA15-0919. Moreover pharmacokinetics data indicated that, either with capsules or tablet, the presence of food increased the systemic exposure to entrectinib and markedly reduced the variability of the systemic exposure to the compound. At the single dose of 60mg/kg as tablets, unchanged entrectinib was found to be the main component and M5 the main metabolite in plasma dogs, with amounts decreasing over time. The systemic exposure to entrectinib was approximately similar after IV or PO 10 mg/kg dose (AUCINF 44.4 and 49.7 µM·hr respectively) while increased considerably to 236 µM·hr, after 100 mg/kg PO dose, with an oral bioavailability ranged between 90% and 40%, following 10-100 mg/kg PO administration. After repeated treatment given twice a day for 5 days to mice at IV 10 and PO 60 mg/kg, non-compartmental and compartmental exposure parameters in terms of AUCs were in good agreement with the ct for tumor stabilisation ranged from 1.20 µM to 0.786 µM and the *in vivo* potency parameter from 0.193 to 0.276 1/µM/day. With non-compartmental PK analysis evaluated after single (1st dose) and repeated (11th dose) 80 and 120 mg/kg bid administration to female mice, the pharmacokinetics of entrectinib have been confirmed to be, dose-proportional. After multiple dosing, minimal accumulation was observed on both Cmax and AUC(0-11). The RA (accumulation ratio) on Cmax was approximately 1.4 while on AUC(0-11) was 1.3 after 80 and 120 mg/kg bid dose, respectively.

2.3.4. Toxicology

Single dose toxicity

Single oral dose toxicity studies were conducted in rats and one dog, the maximum tolerated dose (MTD) exceeded the highest doses tested of 240 and 300 mg/kg, respectively. Decrease in size/number of stools at ≥120 mg/kg and decreased positional passivity at ≥60 mg/kg were observed in rats during the Irwin test. Increased platelets and increased phosphorus and total bilirubin in females were observed at 240 mg/kg. Reduced extra medullary hematopoiesis was also observed in spleen of male rats at the same dose.

In dogs, minimal increase in lactate dehydrogenase and creatine kinase were observed.

Repeat dose toxicity

RATS

Oral administration of etrectinib for four weeks to Sprague Dawley rats at doses of 50, 100 and 200 mg/kg/day caused mortality in females during anesthesia for blood collection. Findings were similar to other animals at this dose and included incoordination, skin ulceration, bile duct epithelial vacuolation, and hyperplasia and macrophage accumulations in the liver and lymphoid tissues. Following 2 week administration at 400 mg/kg/day, dyspnea, hypoactivity and incoordination, marked hepatocellular vacuolation and necrosis, and severe lymphoid depletion were observed.

Effects on CNS

In the 4-week (2x2 intermittent dosing) study at 200 mg/kg/day, incoordination was noted starting on Day 6, and a modified Irwin test showed abnormal gait on day 14.

In a second 4-week daily dose study, no CNS-related clinical signs were noted at 100 mg/kg/day up to 24 days (due to early termination), or at doses ≤50 mg/kg/day up to 28 days.

The same holds true for the 13-week study, where no CNS effects were seen at doses up to the highest dose administered (30 mg/kg/day).

Skin changes

Following 4-week administration with 4-week recovery scabbed areas were observed in both sexes at all doses tested; at 100 and 200 mg/kg/day males showed also ulcerations. In this study, no NOAEL was set, and the MTD was 100 mg/kg/day.

In a second 4 week study with 2-week recovery, skin scabs/sores were noted at all dose levels, with severity and incidence increasing in a dose-dependent manner. These scabs/sores progressed to ulcerative moist lesions requiring veterinary treatment at ≥50 mg/kg. Microscopically, these skin lesions exhibited acanthosis, erosion/ulcer, epidermal surface exudate, hemorrhage, and/or mixed cell inflammation. The skin changes were reversible. The skin lesions, more severe in the female rats, manifested as scabs/sores and ulcerative moist lesions in some cases, coincided with decreased body weight and food consumption in the 100 mg/kg/day females, and correlated microscopically with minimal to marked acanthosis, erosion/ulcer, epidermal surface exudate, hemorrhage, and/or mixed cell inflammation. The skin effects were also reflected in clinical pathology changes indicative of inflammatory response, i.e., higher leukocyte and platelet counts, as well as serum protein changes (low albumin and globulin ratio, and high globulin concentration). Skin lesions resolved during the recovery phase.

Dose-related skin lesions observed at ≥7.5 mg/kg/day after 13-week administration, manifested as scabs/sores (manifested only in females at the 7.5 mg/kg), and ulcerative dermatitis typically on the head, shoulder, and/or cervical region; correlated microscopically with acanthosis, erosion/ulcer, epidermal surface exudate, serocellular crust, hemorrhage, and/or mixed cell inflammation. The skin alterations became dose-limiting and resulted in early sacrifices at the higher doses. However, these resolved upon dosing suspension.

In light of the findings shown above, skin lesions at 15 or 30 mg/kg/day were considered adverse, and 7.5 mg/kg/day was the NOAEL (Day 91: Cmax M/F=0.63/0.63 µM; AUC0-24=5.98/6.71 µM.hr).

Corneal findings

In a 4-week plus 4-week recovery corneal findings, namely opacity area/s either mono- or bilateral, have been observed at the top dose with an incidence higher than expected (8 M and 7 F). Generally this alteration is only sporadically observed and in the vast majority of cases is monolateral. While for

three rats (two M and one F at top dose) eye wound has been marked after blood sampling procedure on Day 16 and 29 – and considered as a consequence of collection from retro-orbital sinus - for the remaining ones an etiopathogenesis should be identified (a total of 12 rats with 8 bilateral involvement), according to the Applicant. Because of the central effects observed in all females and most males at top dose starting from mid of treatment periods and characterised by incoordination and abnormal gait a possibility is that rat eyes were damaged by sawdust particles when animals were slithering in the bedding and/or perhaps related to impaired corneal reflex, as declared by the Applicant.

In the 4-weeks plus 2-week toxicity study, corneal findings (abrasion or white multifocal deposits, unilateral) were noted in two males and one female at ≥50 mg/kg/day: (AUC0–24 M/F=34.7/49.3 µM.hr; Cmax M/F=2.88/3.51 µM), possibly due to scratching because of skin lesions. No histopathological changes were associated with the ocular findings. A decrease in seminal vesicle weights was observed but without any microscopic correlated.

No corneal findings were seen in the 13-week plus 8-week study in rats, nor in all toxicity studies in dogs.

Clinical pathology

In 4-week plus 4 weeks recovery, at ≥50 mg/kg/day minimal to slight reversible decrease in RBC-related parameters with associated increases in reticulocytes was observed at the end of each treatment period. Minimal to slight decreases in lymphocytes were observed at the end of the second treatment period. Changes in the spleen included minimal to moderate lymphoid depletion, increased incidence and/or severity of extramedullary hematopoiesis and congestion of the red pulp. These changes correlated with increased spleen weights seen also at all dose levels. The increased extramedullary hematopoiesis was consistent with the decreased RBC parameters and increased reticulocytes. The lymphoid depletion correlated with decreases in lymphocytes.

Accumulation of foamy macrophages was minimal in the mesenteric lymph of one female at 100 mg/kg, and minimal to moderate in the spleen, mesenteric, and mandibular lymph nodes, liver, and periodontal tissue at 200 mg/kg/day. The macrophages showed similar morphologic characteristics in the various sites and were not accompanied by any signs of degeneration or inflammation.

Minimal to slight changes in the mandibular salivary gland consisted of increased incidence/severity of acinar apoptosis in females ≥100 mg/kg/day and males at 200 mg/kg/day and acinar hypertrophy in both sexes at ≥100 mg/kg/day.

In addition to spleen, minimal to moderate lymphoid depletion was also observed in the mandibular and mesenteric lymph nodes. Increased severity of foamy macrophages occurred in the lungs of animals given 200 mg/kg/day when compared with controls. Slight increases in the incidence and severity of acinar apoptosis were observed in the parotid salivary glands when compared with controls. Minimal to slight myositis of the diaphragm, with some myofiber necrosis/regeneration, was noted in both sexes at 200 mg/kg/day. This change was not observed in subsequent rodent studies with daily dosing for longer periods (4- and 13-week dosing).

In a 4-week plus 2 weeks findings, administration of 50 mg/kg included decreases in RBC counts, hemoglobin, and hematocrit; increases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH); increases in platelet and reticulocyte counts; and higher WBC and neutrophil counts. Changes in the spleen included minimal to moderate lymphoid depletion, increased.

Clinical chemistry findings included lower albumin and albumin:globulin ratio and higher globulin. Minimally higher fibrinogen in females at 25 and 50 mg/kg/day on Day 29 was also consistent with an inflammatory response.

The increase in spleen weights in males correlated with congestion in the red pulp and increased extramedullary hematopoiesis. In addition, the spleen had lymphoid depletion characterised by decreased diameter of the periarteriolar lymphoid sheaths, decreased cellularity of the marginal zone, and decreased cellularity of the red pulp. An observed decrease in mandibular salivary gland weights in 25 and 50 mg/kg/day males did not have a microscopic correlate.

Incidence and/or severity of extramedullary hematopoiesis, and congestion of the red pulp correlated with increased spleen weights at all dose levels. The increased extramedullary hematopoiesis was consistent with the decreased RBC parameters and increased reticulocytes. The lymphoid depletion correlated with decreases in lymphocytes.

Additional hematology changes at 100 mg/kg/day included higher lymphocyte, monocytes, and basophils. In clinical chemistry, changes included higher urea nitrogen, triglycerides, calcium, inorganic phosphorus, ALT, alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and lower chloride levels (males only). No histological findings correlated with the elevated liver enzymes. In the mandibular salivary gland, evidence of increased secretion, characterised by larger acinar cells containing abundant, normal-appearing secretory product, was observed.

In the 13-week one, at ≥15 mg/kg/day, findings in clinical pathology were limited to non-progressive and minor changes primarily in animals at ≥15 mg/kg/day and often increased in magnitude in the early sacrificed animals. Overall, these changes were consistent with an inflammatory response and included minimally lower RBC mass (RBC count, hemoglobin concentration, and/or hematocrit) and mean corpuscular hemoglobin concentration (MCHC), minimally higher MCV and MCH, and mildly to moderately higher reticulocyte absolute counts, minimal or mild increases in leukocyte counts (WBC, monocyte, and neutrophil), minimally higher globulin concentration, and decreased albumin:globulin ratio. Minimally higher platelet count was also considered secondary to increased bone marrow stimulation due to the inflammatory response. These changes correlated microscopically to skin inflammation, extramedullary hematopoiesis in the spleen, and/or hypercellular bone marrow. The hypercellular bone marrow observed at ≥15 mg/kg/day was likely secondary to skin inflammation and increased requirement for inflammatory cells.

Increased spleen weight in males at ≥15 mg/kg/day and females at 30 mg/kg/day correlated with increased extramedullary hematopoiesis.

At 30 mg/kg/day clinical pathology changes that were considered consistent with inflammation included minimally higher fibrinogen concentration in males.

All the findings were reversible or showed a trend towards reversibility.

Lymphoid depletion was observed at ≥25 mg/kg/day in the 4-week study in spleen, and also in lymph nodes and thymus at ≥200 mg/kg/day in the 4-week 2x2 intermittent dosing and 14-day studies. Additionally, decreased bone marrow cellularity was also observed at ≥400 mg/kg in the 14-day study.

Effects on Hepatobiliary System

Hepatocellular findings were mainly observed in the 4-week study with 2x2 intermittent dosing and included dose-related increases in AST (up to 7.3-fold) and ALT (up to 17-fold) at ≥50 mg/kg/day. Increased bilirubin was also observed in rats at ≥50 mg/kg/day in the 4-week 2x2 intermittent dosing study. These serum chemistry changes correlated with increases in the incidence of hepatocellular vacuolation with associated necrosis/single cell necrosis, vacuolation of bile duct epithelium, and minimal biliary epithelial hyperplasia at ≥200 mg/kg/day.

A minimal increase in amylase was seen in females at the end of treatment periods, in the 4 weeks plus 4 week recovery study.

Slight, dose-dependent increases in AST and ALT were observed at all doses at the end of each treatment period, with subsequent recovery. Bilirubin levels were minimally to slightly elevated at the end of the first treatment period, with no dose-response relationship. Lipase levels were marginally increased at the end of treatment periods in a dose-independent manner.

Minimal to moderate vacuolation of the bile duct epithelium occasionally associated with minimal bile duct epithelium hyperplasia was observed in all animals at 200 mg/kg/day.

In addition, minor increases in the incidence of hepatocellular vacuolation, sometimes in association with single cell hepatocellular necrosis, was also observed. These changes correlated, in both sexes, with the increases in serum levels of ALT and AST along with gross enlargement and, in females, increased weight of the liver.

In a second 4 week study, higher ALT, alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and lower chloride levels (males only) were observed following administration of entrectinib 100 mg/kg/day. Histological findings correlated with the elevated liver enzymes.

DOGS

CNS signs

In dogs, CNS effects (incoordination, staggering, abnormal gait, tremors, hypoactivity, depression, lateral recumbency and lethargy) were considered the cause of death or early euthanasia of female animals given 120 mg/kg/day after 10 days of dosing in the 4-week (2x2 intermittent dosing) study.

In the 4-week (2x2 intermittent dosing) study, CNS effects were seen at ≥60 mg/kg/day.

Starting on Days 6 to 7, animals at 120 mg/kg/day had incoordination of hindlimbs and forelimbs, staggering, abnormal gait, tremors, hypoactivity and depression. these signs were particularly severe at the dose of 120 mg/kg/day (AUC0-24: 147-159 μM·h after repeated administration), so to lead to preterm sacrifice or mortality of the majority of females, and to interruption of the treatment at that dose level.

At 60 mg/kg/day, abnormal gait or incoordination and decreased activity were observed during both treatment periods; in addition, slight to moderate increases in activity and/or stereotypy were observed during the second treatment period.

Similar observations were also noted at 120 mg/kg/day in a 7-day exploratory study.

The CNS signs developed from Day 7 and included incoordination of hind limbs and fore limbs, staggering, tremors and hypoactivity.

No CNS effects were observed in other toxicity studies.

Skin findings

In a 4 week study (2x2 intermittent dosing), administration of entrectinib at the mid dose led to skin changes, including abrasions sometimes with ulcerations and crusts, were observed on legs, paws, and eyelids during the second treatment period. Histologically, these lesions were consistent with inflammation characterised by infiltration of neutrophils, lymphocytes, plasma cells, and macrophages together with fibroplasia, edema, and fibrin exudation. These abrasions were reversible during the recovery period.

In the second 4 weeks study, at ≥15 mg/kg/day: (AUC0–24 M/F=2.63/2.57 μM.hr; Cmax M/F=0.341/0.427 μM) broken, discoloration, scabs and/or sores were noted for the skin/subcutis of males at ≥15 mg/kg/day and females at 15 or 30 mg/kg/day. Histologically, these correlated with

ulcer, acanthosis, hyperkeratosis, dermal fibrosis, mononuclear cell infiltrates and neutrophil infiltrates. These changes were reversible.

In the 13 weeks at ≥7.5 mg/kg/day: (AUC0–24 M/F=1.93/1.81 µM.hr; Cmax M/F=0.276/0.226 µM) skin lesions including sores, scab/scaly skin, swollen/raised areas, discolored areas on the foot pads and/or interdigital space leading to limited use of right and/or left front or hindlimbs were observed. These clinical observations showed reversibility at the end of recovery phase. Associated microscopic finding in the skin included erosion/ulcer, acanthosis, and/or acute or mixed cell inflammation.

Hematology and clinical pathology changes

In the 4-Week study in dogs with 2x2 Intermittent dosing schedule, in hematology, minimal to slight increase in platelets were present. Slight to moderate increases (up to 2.4-fold) in ALT were observed. Histologically, slight hepatocellular necrosis in 1 female and minimally increased severity of extramedullary hematopoiesis and pigmented macrophages in the liver of some females were present.

Histopathology findings included minimal to moderate increase of pigmented macrophages in the spleen, most likely laden with hemosiderin (i.e. positive at Perls' stain), and slight to marked congestion in the spleen. Reversible, epithelial hyperplasia in the gallbladder was noted at 30 and 120 mg/kg/day (also with yellowish granular pigment), but was not seen in 60 mg/kg/day animals. An increased incidence of aspiration pneumonia was observed in treated animals.

In the surviving animals that received 120 mg/kg/day, a minimal to slight increase in RBCs, hemoglobin, and hematocrit, and a decrease of reticulocyte counts were observed, followed by partial to complete recovery during the recovery period. A moderate to severe increase (4.3- to 29-fold for individual animals compared with their own pretest values) in ALT and a slight to severe increase (2- to 16-fold for individual animals compared with their own pretest values) in AST, ALP, GGT, and total bilirubin, with subsequent recovery was observed. Minimal to moderate extramedullary hematopoiesis and pigmented macrophages were observed microscopically in the liver and spleen; the spleen also exhibited slight to marked congestion at the end of recovery periods.

At 4 weeks, clinical pathology effects were consistent with an inflammatory response in males dosed at ≥30 mg/kg/day and females at all doses correlating with the findings in the skin and mucocutaneous junction of the rectum. The findings included minimal to mild increases in WBC, neutrophil and monocytes. In addition, increased platelet count in males at 60/45 mg/kg/day and in females at all dose levels was observed. Serum protein changes included mildly to moderately decreased albumin concentrations and mildly to markedly increased globulin concentrations in males given ≥30 mg/kg/day and females at all dose levels, resulting in decreased albumin:globulin ratios at the same dose levels.

An increase in fibrinogen was observed at all dose levels. Mildly increased cholesterol concentrations in animals given ≥30 mg/kg/day were also observed.

Increased liver weights at≥30 mg/kg/day that also persisted into recovery (60/45 mg/kg/day) did not have correlative microscopic findings and/or any correlative clinical chemistry changes. Mildly increased eosinophil counts were observed in males. A mildly increased total protein concentration in females given 60/45 mg/kg/day was observed due to markedly increased globulin concentrations. Additional changes included mildly decreased calcium concentrations in females given 60/45 mg/kg/day, which were attributed to lower albumin concentrations.

In the 13-Week study, entrectinib administration resulted in reversible effects on clinical pathology in animals administered ≥7.5 mg/kg/day consistent with an inflammatory response. These included minimally to mildly increased WBC count, attributed to increased neutrophil count, on Days 40 and 90 of the dosing phase in males administered ≥7.5 mg/kg/day; increased absolute monocyte count on

Days 40 and/or 90 of the dosing phase in males administered ≥7.5 mg/kg/day and females administered 15 or 30 mg/kg/day; and minimally increased total protein concentration, minimally to mildly decreased albumin concentration, mildly increased globulin concentration, minimally to mildly increased fibrinogen concentration, and mildly to moderately decreased albumin:globulin ratio on Days 40 and/or 90 of the dosing phase in males administered ≥7.5 mg/kg/day and females administered 15 or 30 mg/kg/day. Minimally to mildly decreased calcium concentration on Days 40 and/or 90 of the dosing phase in animals administered ≥7.5 mg/kg/day was likely related to decreased albumin concentration. These hematology and clinical chemistry effects correlated with microscopic findings of erosion/ulceration and inflammation in the rectum and skin of foot/foot pads and aspiration-related inflammation in the lungs.

Effects on Gastrointestinal Tract

In the 4-week study, one female at 60 mg/kg was found dead on Day 9, though the cause of death was undetermined the female did show clinical signs of GI toxicity including abnormal (liquid, mucoid and/or abnormal) feces and pathology findings of erosion/ulceration at the mucocutaneous junction in the rectum.

Emesis and diarrhea, sometimes associated with body weight loss and decreased food consumption, were observed in the, 4-week 2x2 intermittent dosing at ≥30 mg/kg/day: (AUC0–24 M/F=20.8/21.1 µM.hr; Cmax M/F=1.68/1.56 µM), diarrhea and soft stool were observed sporadically. In the 4-week study, at ≥30 mg/kg/day: (AUC0–24 M/F=9.13/9.49 µM.hr; Cmax M/F=1.37/1.38 µM) liquid feces were noted, though at a lower incidence than in the high-dose group. At 60/45 mg/kg/day: (AUC0–24 M/F=7.97/10.3 µM.hr; Cmax M/F=1.14/1.63 µM) emesis and/or liquid feces occurred at a greater incidence at 60/45 mg/kg/day and were considered dose-limiting at 60 mg/kg/day.

At 15 mg/kg, microscopically, erosion/ulcer of anal squamous epithelium and/or neutrophil infiltrates in rectum were noted ≥15 mg/kg/day. Abnormal fecal changes associated with body weight loss and decrease in food consumption were considered adverse.

At 30 mg/kg/day: (AUC0–24 M/F=8.04/7.09 µM.hr; Cmax M/F=0.912/0.839 µM) entrectinib caused abnormal feces (discolored [red/black] liquid/mucoid and/or non-formed feces) leading to dosing suspension for two animals for 3 and 6 days, respectively. There was also a correlative body weight loss and a decrease in food consumption.

Additionally, GI toxicity a high incidence of vomiting and diarrhea (with correlative body weight and food consumption change) plus the early death of one female on Day 9, resulted in dosing suspension at 60 mg/kg/day (dose subsequently reduced to 45 mg/kg/day) in the 4-week daily dosing study and dosing suspension for individual animals administered 30 mg/kg in the 13-week study.

QT/QTc Interval Prolongation

In vitro, entrectinib inhibited hERG with an IC50 of 0.6 µM as a free drug, indicating a potential for cardiovascular risk. M5, the major human metabolite, inhibited hERG with an IC50 of >10 µM.

In telemetered dogs, single dose of entrectinib up to 300 mg/kg did not have any effect on cardiovascular parameters including ECG intervals (see safety PD).

In the 4-week (2x2 intermittent dosing) study, moderate prolongation of the QT/QTcF intervals was noted at 120 mg/kg/day (recorded on Day 11), where a Cmax of >7 µM was observed. Compared to the pre-dose data for individual animals, there was a dose-related increase in the incidence. Thus, the observed time- and dose-dependent QTc changes in females were considered entrectinib related.

ECG evaluations conducted on Day 11 in the 120 mg/kg/day group had prolongation of ventricular repolarisation (QT and/or QTcF) in 2 of 5 males (QTcF mean: 29 msec) and 4 of 5 females (QTcF

mean: 80 msec). The 4 females with increased QT/QTcF intervals were the same animals that were later found dead or were sacrificed on Day 13; (the Cmax ranged from 5.6 to 12.6 µM and AUC from 115 to 250 µM.hr in these animals).

In male treatment groups in the 4-week study, no time- or dose-dependent QTc changes were observed. Prolongation of QTcF interval at 4 hours postdose was noted in females at 15 (10 msec, 4%), 30 (23 msec, 10%), or 60/45 mg/kg/day (22 msec, 9%). The QTcF interval was still prolonged on Day 11 of the recovery phase in one surviving 60/45 mg/kg/day female, however, QTcF intervals were also longer in control females during the recovery phase.

No changes in QT/QTcF intervals were detected in the 13-week study at doses up to 30 mg/kg/day (Cmax = 0.9 µM) recorded on Days 40 and 90. An incidental but statistically significant finding not attributed to entrectinib was limited to changes in QTc interval in males. In reviewing individual heart rate, QT interval, and QTc interval data, no consistent trend for QT interval prolongation, relative to predose phase values, was noted compared with heart rate changes. In addition, no test article-related changes in QTc interval were observed during the dosing phase in females administered any dose level, in which mean exposure levels (entrectinib or M5) were similar to those seen in males. In addition, no relationship with dose was seen in the QTc interval changes in individual males administered 30 mg/kg/day. Therefore, the statistical finding for QTc interval in males administered 30 mg/kg/day was considered incidental and not attributed to entrectinib. No rhythm abnormalities or qualitative ECG changes attributed to entrectinib were observed on Day 40 or 90 of the dosing phase or Day 55 of the recovery phase as part of the qualitative assessment of the ECGs.

Borderline first degree atrioventricular block (PR interval ≥ 130 msec; (Tilley and Smith, 2008) was noted predose and approximately 2 hours postdose on Days 40 and 90 of the dosing phase in one animal administered 7.5 mg/kg/day. First degree atrioventricular block is a common arrhythmia in dogs.

Effects on hepatobiliary system

Findings were mainly observed in 4-week study with 2x2 intermittent dosing, mainly at doses ≥MTD. Increases in ALT (4.3- to 29-fold) and AST (2- to 3-fold), ALP, GGT, and total bilirubin were observed at 120 mg/kg/day after 10 or 11 days of dosing. Increases in ALT (up to 2.4-fold) were also observed at 60 mg/kg/day after 2 weeks of dosing. Microscopic findings in the liver included increased severity of pigmented macrophages and extramedullary hematopoiesis, minimal to slight hepatocellular necrosis at ≥60 mg/kg/day, and mitotic figure increase at 120 mg/kg/day. In addition, reversible epithelial hyperplasia in the gallbladder was noted at 30 and 120 mg/kg/day (also with yellowish granular pigment), but was not seen in 60 mg/kg/day animals. Increased liver weights were also observed in both sexes at 60/45 and 30 mg/kg/day in the 4-week study and in 30 mg/kg/day male dogs at the end of 13 weeks of dosing, however, no correlating clinical chemistry or histological findings were noted.

Genotoxicity

Bacterial toxicity of entrectinib was observed both in the absence and in the presence of metabolic activation at concentrations of ≥9.76 and ≥4.88µg/plate and at concentrations of ≥78.1 µg/plate and ≥39 µg/plate. The results suggested that entrectinib did not induce mutations in bacteria under the conditions of this study. In a GLP micronucleus assay in HPBL, a statistically significant and concentration-related increase in the percentage of micronuclei was observed at 15 µg/mL and concurrent cytotoxicity of 53%, following treatment of 24 hours in the absence of S9. No statistically significant increases outside the historical control range were seen at any concentration, following 4 hours of incubation (±S9).

A follow-up experiment at 15 µg/mL (24hr/-S9) applying fluorescence *in situ* hybridisation (FISH) analysis revealed an increase in centromere-positive micronuclei (81%), suggesting an aneugenic mode of action for entrectinib-induced micronucleation.

Moreover, entrectinib was negative in the *in vivo* liver comet and bone marrow micronucleus assays at exposure levels 3.1 - and 3.9-fold (Cmax=10.8 µM; AUC0-t=242 µM.hr, respectively) above the anticipated human exposure (Cmaxss: 3.49 µM; AUCss: 62.8 µM.h).

Carcinogenicity

No carcinogenicity studies have been submitted as part of the application.

Reproduction Toxicity

Entrectinib oral administration to groups of 8 pregnant rats during the organogenesis period, led to reduced maternal body weight gain (without a corresponding reduction in food consumption) observed with the highest dose. Fetal weights were reduced at all dose levels and were statistically significant at 100 and 200 mg/kg/day. There were no entrectinib-related external fetal malformations or variations at any dose level.

In a GLP embryo-fetal development toxicity study in rats, maternal toxicity was apparent at 200 mg/kg/day, as evidenced by adverse clinical signs, as well as lower body weight parameters and corresponding decreased mean food consumption generally throughout gestation. No evidence of maternal toxicity was noted at 12.5 and 50 mg/kg/day.

A dosage level of 50 mg/kg/day was therefore considered to be the NOAEL for maternal toxicity, lower mean fetal weights were noted at 50 and 200 mg/kg/day. These fetal weight effects corresponded to the lower mean gravid uterine weight and increases in external and skeletal malformations at 200 mg/kg/day, as well as the reduced fetal skeletal ossification findings at 50 and 200 mg/kg/day. Based on these results, a dosage level of 12.5 mg/kg/day was considered to be the NOAEL for embryo/fetal developmental toxicity. The corresponding maternal exposures (AUC0-24) of RXDX-101 on gestation day 17 at the maternal NOAEL of 50 mg/kg/day was 41.5 µM*hr, while an AUC0-24 value of 10.2 µM*hr was observed at the embryo/fetal developmental NOAEL of 12.5 mg/kg/day.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

In the tolerability and TK study, repeat entrectinib dosing from PND 7 through 12, led to clinical signs of slight suspected dehydration and moderate reductions in body weight gains, at 50 mg/kg/day. The findings were shown at the top dose of 100 mg/kg/day as well, in addition to cold to touch. Based on these data, dose levels of 0 (Control), 25, 50, and 75 mg/kg/day were recommended for the dose range-finding toxicity study in juvenile rats. However, oral administration by gavage on PNDs 7 through 34 exceeded the MTD at all doses in the dose range finding study. The mortality and severity of toxicities led to early terminations of the animals at 50 mg/kg/day (PND 21 to 22) and 75 mg/kg/day (PND 15 and 17).

Based on these data, dose levels of 4, 8, and 16 mg/kg/day were selected for the definitive toxicity study in juvenile rats. Entrectinib was tolerated in juvenile rats at 8 mg/kg/day but induced mortalities at 16 mg/kg/day. The NOAEL for this study was hence considered to be 4 mg/kg/day, based on the developmental delays, clinical signs including convulsions, abnormal gait, decreased activity, tremors, labored breathing, prostration, low carriage, and increased respiratory rate (breathing), and effects on FOB and water maze at higher doses. The associated AUC0-24 values for entrectinib at 4 mg/kg/day

were 7.48 and 6.05 µM.h on PND 7 and 2.2 and 3.1 µM.h on PND 97 for males and females, respectively.

Toxicokinetic data

The T_{max} in rats ranged from 4-8h. Higher exposure levels were achieved in females (~2x) compared to males. Exposure generally increased in a dose-proportional manner and moderate accumulation (1,2-2x) was observed. In the 4w study (2x2w cycle), entrectinib levels in brain were 40% lower than those in plasma apart from in females at 200mg/kg/day, were comparable levels were measured. The human metabolite M5 was a minor component (0-13% of parent) in rat plasma.

In dogs there were no apparent sex differences in exposure of entrectinib. The T_{max} in dogs ranged from 1-4h at doses up to 60mg/kg/day and 11-12h at higher doses. Exposure generally increased in a dose-proportional manner except in the 13w study in which non-linear toxicokinetics was seen. Accumulation was observed, with the mean accumulation ratio ranging from approximately 2-6. When measured, the half-life was approximately 7h and levels of entrectinib in brain 24h after last treatment were approximately two-fold higher than those in plasma. Metabolite M5 was a major circulating component in dogs with AUC_{0-24} ranging from approximately 1x to 3x of entrectinib. There were no apparent sex differences in M5 levels. Accumulation of M5 was observed in dogs with an accumulation ratio ranging from 1,6 to 3,5.

Local Tolerance

Entrectinib was not irritating to the intact skin of New Zealand White rabbits following a single application of 500 mg for 4 hours. Moreover, it induced a transient irritant reaction of the eye when applied as a single dose of 100 mg/animal to New Zealand White rabbits for 1 hour. A complete reversal of these effects occurred within 7 days.

Other toxicity studies

Impurities

A complete assessment of mutagenic impurities was conducted in accordance with the principles of ICH M7 guideline. Considering the indications for entrectinib, the acceptable levels for mutagenic impurities were conservatively defined based on the ICH M7 less-thanlifetime (LTL) acceptable intakes for a treatment duration of 1 to 10 years (i.e., 10 µg per day for individual impurities, 30 micrograms per day for the total of impurities). Certain impurities determined to have structural alerts using *in silico* analysis were tested in the Ames assay. No *in silico* report was provided.

Based on the assay results, it was concluded that RO7278382, RO7278380, RO7278384, RO7280631, RO7288150, and RO7288613 were negative in the bacterial reverse mutation assay, as no positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation.

A 4-week rat study with neat RO7278383 was conducted to qualify a higher level of RO7278383, as this impurity was observed at levels between the ICH Q3A identification and qualification thresholds (0.10%-0.15%) in early development batches of drug substance produced with early versions of the drug substance manufacturing process. Oral administrations of RO7278383 at doses of 0, 0.33, or 1.0 mg/kg/day to male and female rats (10/sex/dose group) for 4 weeks were well tolerated. No effects were observed at any dose tested in the study. Thus, the NOEL of RO7278383 for 4 weeks of dosing in rats was 1.0 mg/kg/day.

Phototoxicity

In an *in vitro* neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts (3T3 NRU PT), entrectinib was found to have phototoxic potential by the photo irritancy factor and mean photo effect. This was not confirmed in the follow-up *in vivo* rat study in Long-Evans pigmented rats, where entrectinib was determined not to be phototoxic.

However, microscopic findings in rats with or without exposure to light of neutrophil infiltrates of corneal stroma and single cell necrosis of the corneal epithelium at doses ≥100 mg/kg/day were considered entrectinib-related. Since corneal findings were observed in entrectinib-treated rats in the absence of UVR exposure (200 mg/kg), this finding was considered entrectinib-related. No cutaneous responses which could be indicative of phototoxicity, were revealed by dermal examination. Additional histological changes in the cornea consistent with phototoxicity, vacuolation of the corneal epithelium and loss of the corneal endothelium, were not observed in rats treated with entrectinib at 100 mg/kg with UVR exposure or 200 mg/kg/day with or without UVR exposure, further indicating that phototoxicity did not contribute to the entrectinib-related changes in the cornea.

2.3.1. Ecotoxicity/environmental risk assessment

Table 12: Summary of main study results

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)	$DT_{50,\ sediment,\ 20\ °C}$ > 120 d $DT_{50,\ whole\ system,\ 20\ °C}$ > 120 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)	3 (default) 0.012 (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	$DT_{50,\ water,\ 20\ °C}$ = 0.8–1.1 d $DT_{50,\ sediment,\ 20\ °C}$ = 12.6–24.5 d $DT_{50,\ total\ system,\ 20\ °C}$ = 4.9–5.1 d Taking into account the high adsorptive properties of Entrectinib and the high non-extractable residues (NER) formation, it has to be assumed that the respective DT50 values for sediment and total system are >120 d % shifting to sediment = 86.7/97% Transformation product >10%: U8 (not identified)			vP
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *Desmodesmus subspicatus*	OECD 201	NOEC	197	µg/L	geometric mean measured concentration (GMC)
Daphnia sp. Reproduction Test	OECD 211	EC_{10}	64.5	µg/L	Time-weighted average concentration (TWA)
Fish, Early Life Stage Toxicity Test / *Danio rerio*	OECD 210	LC_{10}	6.06	µg/L	Mean measured concentration (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 L/kg L/kg L/kg	%lipids: 15.0
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]-labeled 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, Avena sativa and Allium cepa*	OECD 208	NOEC	1,000	mg/ kg	
Chronic toxicity to Earthworm/*Eisenia andrei*	OECD 222	NOEC	100	mg/ kg	dw
Collembola, Reproduction Test/*Folsomia candida*	OECD 232	EC_{10}	108.9	mg/ kg	dw
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	EC_{10} *(corrected to 10% Corg)*	5682	mg/ kg	

2.3.2. Discussion on non-clinical aspects

Pharmacology

Overall, non-clinical anti-tumoral activity of entrectinib was demonstrated in four *in vitro* cell-based model (BCAN - NTRK1, NPM - ALK, EML4 – ALK, TEL - ALK) and six *in vivo* (TPM3 - NTRK1, ETV6 - NTRK3, CD74 - ROS1, NPM – ALK, EML4 - ALK) xenograft model. Protein sequencing conservation of NTRK genes, ROS1, and ALK between humans and animals makes the mouse the most appropriate species to assess primary pharmacodynamics effects of entrectinib. Sequence comparisons showed 100% or near 100% sequence homologies in the entrectinib binding site, building confidence on the theoretical validity of the selected species used for the safety validation. Although, it cannot entirely be excluded, sequence differences outside the binding region affect the 3D conformation of the binding region, the occurrence of CNS effects indicative of pharmacodynamically mediated effects together with the sequence homologies indicates that entrectinib was pharmacologically active in the toxicology species.

Biochemical characterisation displayed that entrectinib is a strong and selective inhibitor of TRKA, TRKB, TRKC, ROS1, and ALK kinases with comparable IC50 values. Anti-proliferative activity (IC50 < 1μM) of entrectinib and the major active metabolite M5 was observed *in vitro* in 21 cancer cell lines of which five unique NTRK fusion cell, four unique ROS1 fusion cell lines including five ALK dysregulated cell lines, and NCI-H2228. Selectivity was proven in Ba/F3 cell lines transformed by NTRK1, NTRK2, or NTRK3 fusions with various fusion partners: entrectinib was highly potent in all TRK-fusion driven cell lines tested, inhibiting proliferation with IC50 values <6 nM, but not in the Ba/F3 parental line (control - IC50 >1000 nM).

Consistently with *in vitro* data, both entrectinib and M5 treatments showed potent and dose-dependent anti-tumor activity consistent in tumour stabilisation and regression with doses greater than 1 mg/kg. No *in vivo* studies were performed on xenograft models harbouring NTRK2 fusions that appears to be the less represented in NTRK solid tumour types included in clinical efficacy analysis set (54 patients): the majority of patients enrolled in clinical trials had NTRK3 fusions (57.4%), NTRK1 fusions were reported in 38.9% of patients and NTRK2 fusions were reported for 1 patient (1.9%). Although the most common fusion partner identified in clinical studies was ETV6-NTRK3 in 25 patients (e.g. mammary analogue secretory carcinoma of the salivary glands, secretory breast carcinoma), no *in vivo* study with the clinical histologies carrying the ETV6-NTRK3 rearrangement, was performed. It is therefore not possible to understand whether any direct concordance between non-clinical and clinical data in terms of tumour site, ETV6-NTRK3 fusion type, patient age, exists. No other NTRK3 fusions were tested in *in vivo* models.

In light of the claimed site and histology independent indication, the non-clinical pharmacological data-package is considered insufficient to extrapolate activity in all clinical TRK fusions and tumour histologies including paediatric tumours. From a non-clinical point of view, entrectinib demonstrated response towards 9 TRK1,3-driven and 3 ROS1-driven tumour models (both cell-based and patient-derived xenografts of which only 1 orthotopic model for glioma), representing 5 solid tumour types (sarcoma, head and neck squamous cell carcinoma, NSCLC, CRC, glioma) and 1 haematological tumour (AML), and 8 gene fusions (5 TRK1,3 and 3 ROS1). An additional in vivo model, SY5Y-TRKB (TRKB overexpression) neuroblastoma (NB) cell line-derived xenograft was used (Iyer et al. 2016). NTRK2 was over-expressed and observed and high expression of full length TRKB led to activation of ligand-driven (brain-derived neurotrophic factor [BDNF]) activation of TRKB phosphorylation and downstream pathway activity. There is interesting preclinical evidence for the use of entrectinib in the treatment of NB, particularly in patients with TRK, ALK and ROS1 tyrosine kinases alterations. However the clinical efficacy in NB remains under investigation and additional clinical data are needed, both as a single agent and in combination, to

determine whether entrectinib is a beneficial and tolerable therapy for NB and which subset of patients is most likely to benefit.

Selectivity towards NTRK and ROS1 fusions was only assessed *in vitro* on a panel of a number of kinases.

Investigation of recurrent fusion partners in tumour types where NTRK fusions are rare, did not achieve further insight regarding tissue or fusion partner as effect modulators.

Although the proof of concept demonstration in relation to histology-independent indications should in principle not be different from classical approach of anticancer drugs, it is understood that it is not possible to reflect with non-clinical models the wide clinical pattern in terms of tissue environment and pathophysiological context including gene fusion events. This is particularly relevant for rare cancer types for which entrectinib is seeking approval.

The Applicant is recommended to use the mouse Ba/F3 pro-B cell line model to further assess and clarify oncogenic activity of novel NTRK fusions identified in the patient samples obtained in the pivotal clinical studies; the aim should be to understand biochemical events in NTRK fusion samples from patients not achieving clinical response.

Compared to the ROS1 inhibitor crizotinib and the investigational ceritinib in the Phase 2 clinical trials, entrectinib resulted more potent with an anti-proliferation activity IC50 of 20.1 nM. In a panel of 160 cell lines of diverse histological origins, entrectinib exhibited a IC50 ranged between 0.020 to 0.081μM. *In vivo* entrectinib caused dose-dependent TGI in a variety of ROS1 and ALK gene rearrangement-positive models including allografts expressing crizotinib-resistant ALK mutations. Tumour regression has been observed in both models starting from doses of 15 mg/Kg.

Childhood cancers include many cancers that also occur in adults. The anti-proliferative activity of entrectinib was tested in a panel of 303 cell lines including 39 paediatric cancer cell lines, even if the applicant did not specify which tumours have been taken into account to understand their frequency into the paediatric population. Moreover in adult malignancies, TRK fusions have been detected across a broad range of histologies at low frequency (less than 1%). Most paediatric cancers have not been sufficiently evaluated to exclude the presence of TRK fusions at this prevalence (Catherine. et al., 2018) that could represent an important relationship with relapsed or refractory solid tumours in children.

Additionally literature data reported that the response to entrectinib is limited in time due to acquired resistance following development of mutations that make kinases insensitive to the treatment. In a NTRK1 Fusion-Positive tumor cell brain metastasis–mimicking model obtained through injection of KM12SM cells, has been found that the NTRK1-G667C mutation caused entrectinib resistance in brain lesions (Akihiro et al, 2018). Moreover, LMNA-NTRK1—positive CRC from patients and the TPM3-NTRK1—positive colon cancer cell line KM12 acquired entrectinib resistance through acquisition of two point mutations in the catalytic domain of NTRK1, G667 and G595R respectively (Russo et al., 2016). Based on these assumptions, identification of any biomarkers that would confer lack of response in certain patients is relevant (see recommendation above).

In vitro screening assays investigated the secondary pharmacodynamic effects of a single concentration (10 μM) of entrectinib and its major metabolite M5 on ligand binding to 89 targets. The results of these assays showed significant binding (≥50%) at concentrations far exceeding the highest clinical entrectinib and M5 plasma concentration against several targets.

Safety pharmacology studies were performed *in vivo*, in dogs and rats after single or repeated oral administration and *in vitro* on cells expressing the human ether-a-go-go-related gene (hERG). Entrectinib effects were evaluated on the cardiovascular/central nervous and respiratory systems.

It is noted, the *in vitro* hERG assay, in the safety pharmacology package and reported in study 1087275, was carried out under non-GLP conditions. It should have been conducted according to GLP, as stated in

ICH-S7B. However, since QT prolongation have been observed in the clinical studies, the absence of GLP conditions in this *in vitro* hERG assay does not warrant any further action.

Pharmacokinetic

Absorption, distribution, metabolism, and excretion (ADME) studies for entrectinib have been conducted in mice, rats and dogs. The studies were carried out primarily with oral administration, which is the proposed clinical route of administration. Pharmacokinetic analysis following repeated doses was performed in pharmacology studies 1090134 - 1090136 in mice and in all repeated-dose toxicology studies.

In all GLP studies rat and dogs plasma concentrations of entrectinib and M5 were measured using a validated LC-MS/MS-based bioanalytical method. The LC-MS/MS methods used in non-GLP nonclinical studies were either validated or qualified. The validated assays were reliable as no significant deviations from GLP principles or SOPs were reported that could have a potential impact on the reliability of the validation and resulting PK/TK analysis. The fact that the validation of the assays was not conducted under a formal claim of GLP is considered to have no adverse impact on the quality of the validation of the methods, and hence on the resulting PK/TK analysis. Non-validated LC-MS/MS methods were also developed and used for the analysis of plasma and brain samples for preliminary or exploratory PK studies in mice, rats and dogs. In addition, radioactivity levels were measured in blood, plasma, urine, and faecal samples from mass balance studies in rats and dogs. For all validated methods the quantification range, and the intra- and inter-assay accuracy and precision were within ±15% and ≤15% coefficient of variation [CV], respectively, and ± 20% and ≤20% CV at lower limit of quantification [LLOQ], respectively. The methods of analysis are considered as suitable for purpose.

The absorption characteristics of entrectinib has been adequately studied. Entrectinib was extensively bound to plasma proteins in animals and human. Entrectinib resulted widely distributed into tissues.

Contrasting findings were reported on the levels of entrectinib found in the CNS (subsequently to passing the BBB), depending on which method that was used. In the QWBA the total radioactivity in CNS tissues were below the detection limit, as compared to the LC-MS/MS detection in homogenised brain tissue, where entrectinib could be detected at approximately 20% of plasma exposure. In addition, after repeated oral doses brain-to-plasma concentration ratios of entrectinib were higher at 24 hours post last dose in mice (~0.4), rats (0.6–1.5), and dogs (1.4-2.2), indicating brain penetration occurred under steady-state conditions. Furthermore, the brain-to-plasma entrectinib concentration ratio of 0.6 was achieved after a 6-hour infusion of entrectinib to rats even though steady state was still not reached demonstrating that entrectinib can penetrate CNS with low Permeability-glycoprotein (P-gp) efflux effect at the BBB. It appears QWBA is a less adequate method for detection of BBB passage of compound when the establishment of plasma/brain equilibrium is slow.

The main metabolite M11, a direct N-glucuronide conjugate only detected in man and considered inactive was not further studied. This is considered acceptable.

The majority of entrectinib is eliminated as metabolites via the faecal route and urinary excretion plays a minor role in the elimination of [^{14}C]entrectinib-derived radioactivity in both rat and dog.

Toxicology

Entrectinib-related toxicities in repeat-dose studies in adult rats and dogs, and juvenile rats were observed in the CNS (convulsions, abnormal gait, tremors) at ≥0.2 times the human exposures by C_{max} at the recommended dose, skin (scabs/sores) and decreased RBC parameters at ≥0.1 times the human exposure by AUC at the recommended dose. In adult rats and dogs, effects on liver (increased ALT and hepatocellular necrosis) were observed at ≥0.6 times the human exposure by AUC at the recommended dose. In dogs, diarrhoea at ≥0.1 times the human exposure by AUC at the

recommended dose and prolongations of QT/QTc interval at ≥0.1 times the human exposure by C_{max} at the recommended dose were also observed.

Entrectinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay, but demonstrated a potential for abnormal chromosome segregation (aneugenicity) in cultured human peripheral blood lymphocytes. Entrectinib was not clastogenic or aneugenic in the *in vivo* micronucleus assay in rats and did not induce DNA damage in a comet assay in rats.

No carcinogenicity studies have been performed to establish the carcinogenic potential of entrectinib.

Dedicated fertility studies in animals have not been performed to evaluate the effect of entrectinib. No adverse effects of entrectinib on male and female reproductive organs were observed in the repeatdose toxicology studies in rats and dogs at approximately 2.4-fold and 0.6-fold, respectively, the human exposure by AUC at the recommended human dose.

In an embryo-foetal developmental study in rats, maternal toxicity (decreased body weight gain and food consumption) and foetal malformations (including body closure defects and malformations of the vertebrae and ribs), were observed at 200 mg/kg/day of entrectinib which represents approximately 2-fold the human exposure by AUC at the recommended dose. Dose-response dependent reduced foetal body weight (low, middle and high dose) and reduced skeletal ossification (middle and high dose) were observed at exposures equivalent to <2 times the human exposure by AUC at the recommended dose.

In a 13-week juvenile rat toxicology study animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood in humans). In addition to CNS effects, ptosis and skin effects, decreased RBC parameters and effects on growth and development were observed in the dosing and recovery phases including decreased body weight gain and delayed sexual maturation (at ≥ 4 mg/kg/day, approximately 0.1 times the human exposure by AUC at the recommended dose). Deficits in neurobehavioral assessments including functional observational battery (decreased landing foot splay, decreased fore and hind limb grip strength that seemed to manifest later in age) and learning and memory (at ≥ 8mg/kg/day, approximately 0.2 times the human exposure by AUC at the recommended dose), and decreased femur length (at ≥ 16 mg/kg/day, approximately 0.3 times the human exposure by AUC at the recommended dose) were observed (see section 5.3 of the SmPC).

There are no available data from the use of entrectinib in pregnant women. Based on animal studies and its mechanism of action, entrectinib may cause foetal harm when administered to a pregnant woman. Women of childbearing potential must use highly effective contraception methods during treatment and up to 5 weeks after the last dose of entrectinib. Male patients with female partners of childbearing potential must use highly effective contraceptive methods during treatment with Rozlytrek and for 3 months after the last dose (see sections 4.4, 4.5, 4.6 and 5.3 of the SmPC).

The overall assessment indicated that no additional toxicity studies are required to qualify the impurities.

In vitro, entrectinib was demonstrated to be phototoxic. *In vivo*, microscopic findings observed in the corneal stroma and epithelium were indicative of an entrectinib-related effect.

Environmental risk assessment

According to the test on Aerobic and Anaerobic Transformation in Aquatic Sediment Systems (OECD 308), Entrectinib is classified as very persistent in sediment and the whole system. Moreover, according to OECD 305 study results, Entrectinib could meet the criteria for a (very) persistent, bioaccumulative and toxic (PBT) and would therefore be classified as PBT substance. Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see section 6.6 of the SmPC).

2.3.3. Conclusion on the non-clinical aspects

Results from the *in vitro* and *in vivo* pharmacology studies demonstrated that entrectinib is a strong and selective inhibitor activity of kinases TRKA, TRKB, TRKC, ROS1, and ALK with anti-tumor potency in NTRK and ROS1 fusion-driven models driving tumour regressions across multiple tumours types, including 9 TRK1,3-driven and 3 ROS1-driven tumour models (both cell-based and patient-derived xenografts of which only 1 orthotopic model for glioma), representing 6 solid tumour types (sarcoma, head and neck squamous cell carcinoma, NSCLC, CRC, glioma and neuroblastoma) and 1 haematological tumour (AML), and 8 gene fusions (5 TRK1,3 and 3 ROS1). Selectivity towards NTRK and ROS1 fusions was only assessed *in vitro* on a panel of a number of kinases.

The Applicant is recommended to further assess and clarify oncogenic activity of novel NTRK fusions identified in the patient samples obtained in the pivotal clinical studies and to understand biochemical events in NTRK fusion samples from patients not achieving clinical response, using the mouse Ba/F3 pro-B cell line model. Entrectinib and M5 were highly protein-bound (>99%) and entrectinib is capable of penetrating the blood-brain barrier showing anti-tumor activity in multiple intracranial tumors models.

The entrectinib toxicity studies were conducted in compliance with ICH S9 guideline. In general, entrectinib-related effects in repeat-dose toxicity studies either reversed fully (CNS, QT/QTcF prolongation, and GI) or showed a trend towards reversibility (skin, liver and hemolymphopoietic) following the cessation of entrectinib administration. Effects on growth and development were present after the recovery period in the 13-week rat juvenile toxicology study have been reflected in section 5.3 of the SmPC and a relevant warning addressed to pregnant women and women of childbearing potential has been included in section 4.4 and 4.6 of the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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

Table 13: Overview of clinical studies with entrectinib pharmacokinetic and pharmacodynamic data

Study/ Protocol No. (*Country*)	Study Objective	Study Design	Population N (no. of treated subjects)	Dosing Regimen, Formulation	Analysis (CCoD/LPLV)[a]
Clinical Safety and Efficacy Studies					
ALKA-372-001 (ALKA) *(Italy)*	To determine the first cycle DLTs and MTD under 3 different schedules To evaluate the safety profile, PK, and antitumor activity	Phase I, single-arm, open-label, dose-escalation study	Adult patients with advanced/metastatic solid tumors with NTRK, ROS1, or ALK molecular alterations N=57	Entrectinib p.o. QD with F1 formulation using the following schedules: **Schedule A:** 100, 200, 400, 800, 1200, or 1600 mg/m²/day (BSA-based), 4-days on, 3-days off schedule for 3 weeks, followed by a 7-day rest period in a 4-week cycle; fasted. **Schedule B:** 200 or 400 mg/m²/day (BSA-based) or 600 mg/day (flat) in a continuous daily dosing regimen in 4-week cycles; fed. **Schedule C:** 400 or 800 mg/m²/day (BSA-based) 4-days on, 3-days off schedule in a 4-week cycle; fed.	Interim Analysis Study Ongoing (31 May 2018 [c])
RXDX-101-01 (STARTRK-1) *(United States and South Korea)*	Dose escalation: To determine the first cycle DLTs, MTD, and biologically effective and RP2D of entrectinib. To determine safety profile, PK, PD, antitumor activity, biomarkers. Dose expansion: To determine efficacy, intracranial tumor response in CNS patients, safety and tolerability, PK, PD, biomarkers	Phase I, single-arm, multicenter, open-label, dose escalation and expansion study	Adult patients with solid tumors; tumors harboring NTRK, ROS1, or ALK molecular alterations mandatory for the dose expansion phase, but not for the escalation phase N=76	**All cohorts:** entrectinib p.o. once daily (fed) in a continuous daily dosing regimen for 28 consecutive days • 100, 200, 400 mg/m²/day (BSA-based); F1 formulation • 800 mg/day (flat) F1 • 600 mg/day if BSA ≤ 1.85 m² F1; 800 mg/day if BSA > 1.85 m² F1 • 600 mg/day (flat) F1, F2A formulations	Interim Analysis Study Ongoing (31 May 2018)

Study/ Protocol No. (*Country*)	Study Objective	Study Design	Population N (no. of treated subjects)	Dosing Regimen, Formulation	Analysis (CCoD/LPLV)[a]
RXDX-101-02 (STARTRK-2) *(Global)*	To determine efficacy (also CNS separately). To assess safety, tolerability, population PK, ventricular repolarization, patient-reported outcomes	Phase II, global, single-arm, open-label, multicenter basket study	Adult patients with solid tumors with NTRK, ROS1, or ALK gene rearrangements (fusions) excluding ALK-positive NSCLC unless they had had CNS-only progression and had been previously treated with crizotinib; N=206	600 mg entrectinib p.o. QD F2A formulation (4 patients received F1) (fed), in a continuous daily dosing regimen in 4-week cycles	Interim Analysis Study Ongoing (31 May 2018)
RXDX-101-03 (STARTRK-NG) *(United States)*	To determine the MTD or RP2D of entrectinib in children, adolescents, and young adult patients with relapsed or refractory solid extracranial tumors (Part A, other parts included CNS tumors) To determine safety profile, PK, efficacy parameters, intracranial tumor response in CNS patients, biomarkers	Phase I/Ib, single-arm, multicenter, open-label, 5-part, dose escalation and expansion study	Children, adolescents, or young adults with relapsed or refractory solid tumors and primary CNS tumors, with or without NTRK, ROS1, or ALK fusions/molecular alterations N=16	Entrectinib p.o. QD (fed) with F1 formulation (3 patients received F2B), in a continuous daily dosing regimen with 4-week cycles Dosing as per nomogram ranging from 250–750 mg/m²/day	Interim Analysis Study Ongoing (31 May 2018)
Clinical Pharmacology Studies					
CA14707 *(United States)*	Assessment of effect of food, formulation (F1, F2, F2A, F2B), and concomitant lansoprazole on the PK and relative bioavailability of single-dose entrectinib. [b]	Phase I, open-label, randomized, 3-part, 2-sequence, 4-treatment, 3-period study	Healthy adult male and female (of non-childbearing potential) N=72	Single p.o. dose fed or fasted, w/ or w/o PPI; (30 mg lansoprazole QD × 8d or 9d) Part 1: Entrectinib 800 mg F1/F2 formulations Part 2: Entrectinib 800 mg F2A Part 3: Entrectinib 800 mg F2B	Completed (09 Nov 2015)

RXDX-101-04 *(United States)*	To evaluate dose proportionality and compare the relative bioavailability of entrectinib in healthy Japanese and Caucasian subjects after administration of single doses of 400 mg and 600 mg under fasting conditions and 600 mg under fed conditions and to assess the effect of food on the bioavailability of a single dose of entrectinib.[b]	Phase I, open-label	Healthy adult male Japanese and Caucasian N=24	Single p.o. dose of 400 mg F2A and 600 mg F2A entrectinib (fed/fasted)	Completed (12 Feb 2016)

Study/ Protocol No. (*Country*)	**Study Objective**	**Study Design**	**Population N (no. of treated subjects)**	**Dosing Regimen, Formulation**	**Analysis (CCoD/LPLV)[a]**
RXDX-101-05 *(United States)*	To investigate the route(s) of elimination and mass balance of entrectinib after oral administration of a single 600 mg (~200 µCi) dose of [^{14}C]-entrectinib in healthy, adult, male subjects. To quantitate the total radioactivity concentration equivalents in plasma, whole blood, urine, and feces and entrectinib concentrations in plasma and urine after oral administration of a single 600 mg (~200 µCi) dose of [^{14}C]-entrectinib in healthy, adult, male subjects. To examine the metabolic profile of entrectinib in humans and to identify major metabolites in biological specimens. To determine the percentage of [^{14}C]-radioactivity associated with cellular components in whole blood over time (eg, whole blood:plasma partitioning ratio). [b]	Phase I, open-label, 1-period	Healthy adult male N=7	Single p.o. dose of 600 mg [^{14}C]-entrectinib (~200 µCi) as PiC (fasted) plus 246 mg betaine-HCl	Completed (14 Apr 2016)

RXDX-101-06 (*United States*)	To assess the relative bioavailability of a single oral dose of entrectinib F400 granules vs. entrectinib F1 capsules under fed conditions Secondary: To assess the relative bioavailability of a single oral dose of entrectinib F400 granules when administered with yogurt or directly to mouth under fasting or fed conditions.[b]	Phase I, open-label, 2-cohort, 4-period, 4-treatment	Healthy adult male N = 16	Treatment A: single p.o. dose of 400 mg entrectinib (F400 granules) in yogurt (fed) Treatment B: single p.o. dose of 600 mg entrectinib (F400 granules) in yogurt (fed) Treatment C (reference): single p.o. dose of 600 mg entrectinib (3 x 200 mg F1 capsules) (fed) Treatment D: single p.o. dose of 600 mg entrectinib F400 granules in yogurt (fasted) Treatment E: single p.o. dose of 400 mg entrectinib (F400 granules) directly to mouth (fed) Treatment F: single p.o. dose of 600 mg entrectinib F400 granules directly to mouth (fasted)	Completed (31 Dec 2017)

Study/ Protocol No. (*Country*)	**Study Objective**	**Study Design**	**Population N (no. of treated subjects)**	**Dosing Regimen, Formulation**	**Analysis (CCoD/LPLV)[a]**
RXDX-101-07 *(United States)*	To assess the relative bioavailability of a single oral dose of entrectinib formulations (F05, F06, or F07 versus F2A) under fasting conditions in healthy adult male subjects Exploratory: To assess effect of food on a single oral dose of entrectinib (F05, F06, F07, F2A). [b]	Phase I, open-label, comparative, randomized, 4-sequence, 5-period	Healthy adult male N=48	Single p.o. dose of 600 mg entrectinib (fasted/fed) using the formulations (F05, F06, F07, F2A)	Completed (28 June 2017)
RXDX-101-08 *(United States)*	To assess the relative bioavailability of a single oral dose of entrectinib F06 Lot A versus F06 Lot B under fasting conditions in healthy adult male subjects. [b]	Open-label, randomized, 2-period, 2-way crossover study	Healthy adult male N=24	Single p.o. dose of 600 mg entrectinib F06 Lot A (manufactured at registration scale) and F06 Lot B (manufactured at 1/6th of registration scale) (fasted)	Completed (14 Dec 2017)
RXDX-101-09 *(United States)*	To assess the relative bioavailability of a single dose of entrectinib F06 formulation under fasting conditions, when administered with or without multiple daily doses of lansoprazole in healthy adult male subjects. [b]	Phase I, open-label, randomized, 2-period, 2-way crossover	Healthy adult male N=19[c]	Single p.o. dose of 600 mg entrectinib (fasted) F06 formulation with or without 30 mg of lansoprazole delayed-release QD × 9d administered concomitantly.	Completed (12 Jan 2018)

RXDX-101-12 *(United States)*	To assess the effects of itraconazole as a strong CYP3A4 inhibitor and rifampin as a strong CYP3A4 inducer on the PK of entrectinib. [b]	Phase I, open-label, non-randomized, fixed-sequence, 2-cohort	Healthy adult male N = 20	Cohort 1 Period 1: Single p.o. dose of 100 mg entrectinib F06 (fasted) Cohort 1 Period 2: Single p.o. dose of 100 mg entrectinib F06 (fasted) plus itraconazole 200 mg p.o. QD × 10d Cohort 2 Period 1: Single p.o.dose of 600 mg entrectinib F06 (fasted) Cohort 2 Period 2: Single p.o. dose of 600 mg entrectinib F06 (fasted) plus rifampin 600 mg p.o. QD × 16d	Completed (20 Dec 2017)
RXDX-101-13 *(United States)*	To evaluate the effect of entrectinib on the single-dose PK of digoxin. [b]	Phase I, open-label, non-randomized, fixed-sequence	Healthy adult male N = 10	Single p.o. dose of 0.5 mg digoxin with or without single p.o. dose of 600 mg entrectinib F2A (fasted, 1 hour before digoxin)	Completed (13 Oct 2017)
RXDX-101-14 *(United States)*	To evaluate the effect of multiple doses of entrectinib on the single-dose PK of midazolam and the pharmacologically active midazolam metabolite 1-hydroxymidazolam.	Phase I, open-label	Patients with advanced or metastatic solid tumors who may or may not have NTRK, ROS1, or ALK molecular alterations N=13 [d]	Three p.o. doses of 2 mg midazolam on Day 1, 8, and 21 (fasting); continuous administration of 600 mg entrectinib F06 formulation from Day 8 though to Day 22 (fed, except for Day 8 and 21 on which entrectinib is administered under fasting conditions).	Ongoing (16 Jul 2018)
RXDX-101-15 *(United States)*	To assess the relative bioavailability of a single oral dose of entrectinib F06 versus entrectinib F2A under fasting conditions in healthy adult male subjects. To assess the effect of a high-fat meal on the PK of a single oral dose of entrectinib F06 in healthy adult male subjects. [b]	Phase I, open-label, randomized, 2-part, 2-period	Healthy adult male N = 83	Part 1: Single p.o. dose of 600 mg entrectinib (fasted) F06 and F2A in separate periods, respectively. Part 2: Single p.o. dose of 600 mg entrectinib F06 (fasting) and F06 (fed) in separate periods, respectively.	Completed (06 Jun 2018)

BID = twice a day; CCoD = clinical cut-off date; BSA = body surface area; DBL = database lock; DLT = dose-limiting toxicity; LPLV = last patient last visit; PiC = powder in capsule; MTD = maximum tolerated dose; PD = pharmacodynamics; PK = pharmacokinetics; p.o. = per os; QD = once daily; RP2D = recommended Phase II dose.

Notes: F1, F2, F05, F06, F07, F2A, F2B, F400 refer to specific formulations, respectively.

[a] For ongoing studies CCoD/DBL is given, for completed studies LPLV is given.

[b] Evaluation of safety and tolerability of entrectinib under the respective conditions were secondary objectives.

[c] One subject received lansoprazole, but not entrectinib, i.e. 19 subjects received entrectinib and 20 lansoprazole.

[d] Of the 15 enrolled patients, 13 patients received entrectinib, 14 patients midazolam, and 1 patient received no study treatment.

[e] The cut-off date for PK data was 1 May 2017.

2.4.2. Pharmacokinetics

Bioanalysis

Entrectinib (and M5) concentrations were determined in human plasma and excreta using LC-MS/MS following protein precipitation extraction.

Non-compartment data analysis

Standard non-compartmental analysis was performed in all studies where rich sampling was applied.

Physiologically based pharmacokinetic analysis

Physiologically-based pharmacokinetic (PBPK) modelling using the GastroPlus and SimCYP software were utilised to integrate available *in vitro* nonclinical and clinical data and to support the development of entrectinib by assisting the interpretation of clinical studies, predict drug-drug interactions and guide dosing recommendations in children < 4 years of age.

Population pharmacokinetic analysis

A mixed-effects modelling approach has been used to perform population pharmacokinetic (popPK) and population pharmacokinetic/pharmacodynamic (popPK/PD) analyses using data from three Phase I/II studies in 276 adult and paediatric patients with solid malignancies: STARTRK-1 (N=57), STARTRK-2 (N=203), and STARTRK-NG (N=16).

A joint model capturing the PK of both entrectinib and M5 was defined as a default preferred option as both were highly correlated active moieties. To avoid parameter identifiability issues, it was assumed

that all entrectinib was metabolised into M5. Allometric coefficients of 0.75 for the CL/F and 1 for the V/F were used.

Absorption

A mass-balance study RXDX-101-05 was submitted in which 7 healthy subjects were enrolled and received 600 mg [14C]-entrectinib. Blood samples were collected up to 144 hours post-dose, urine and faces were collected up to 24 hours post-dose and until subjects meet the discharge criteria. Sixty-six percent (66%) of Entrectinib was absorbed and data from permeability studies in Caco-2 cells and cells expressing P-gp transporter indicates that entrectinib is not highly permeable. Moreover, in Caco-2 cells the efflux ratio is >2 and the addition of Cyclosporin A decreased the efflux ratio from 4.22 to 0.808 indicating that the transport is mediated by transporters. Data from *in vitro* study 1088452 showed that P-gp mediated entrectinib and M5 transport. From solubility and *in vitro* permeability assessments, entrectinib is defined as BCS Class IV.

Following a single 600 mg oral administration of Rozlytrek to patients with *NTRK* gene fusion-positive and *ROS1*-positive NSCLC under fed conditions, entrectinib was rapidly absorbed reaching time-to-maximum plasma concentration (T_{max}) after approximately 4 to 6 hours. Based on population pharmacokinetic analysis, steady-state was achieved within 5 days for entrectinib with 600 mg once daily dosing.

No clinically significant effect of food on entrectinib bioavailability was observed.

Distribution

After a single oral dose of entrectinib, the geometric mean volume of distribution (Vz/F) was 600 L, suggesting extensive distribution of the drug. Entrectinib demonstrated steady-state brain-to-plasma concentration ratios of 0.4 - 2.2 in multiple animal species (mice, rats, and dogs) at clinically relevant systemic exposures. Entrectinib and M5 are highly bound with plasma proteins (>99%) independent of drug concentrations.

Elimination

The main elimination route was hepatic metabolism via CYP3A4 enzyme and excretion of entrectinib and metabolites in faeces. The terminal half-life of entrectinib in subjects volunteers estimated using NCA methods is approximately 20 h, while the corresponding estimated half-life of M5 is approximately 40 h. Population PK analysis estimated apparent clearance CL/F was 19.6 L/h and 52.4 L/h for entrectinib and M5, respectively.

Mass-balance

In ADME study a total of approximately 86% radioactivity was recovered in urine and feces following the oral administration of a single oral dose of [1^4C]entrectinib to healthy male volunteers over the 312-hour collection period (36% of the dose as unchanged entrectinib and 22% as M5). A mean of 3.06% of the dose was recovered in urine and 82.9% was recovered in feces through the last collection interval, indicating that the main elimination pathway of entrectinib is trough metabolism.

Metabolism

Only 0.3% of the administered dose was retrieved in urine as parent entrectinib. When metabolite profiling of urine was performed, 0.6% of the dose was identified as entrectinib in urine, and most of

the resulting material in urine was identified as metabolites. 36% of the dose was retrieved unchanged in faeces. 50% of the dose was found as metabolites in faeces, the most abundant was M5 (22% of dose), followed by M1 (14%) and M2 (9%).

Metabolite profiling of plasma was performed in the 0-24 hours time-frame, where parent compound accounted for 69% of the AUC, M5 for 12% and M11 for 19%.

Entrectinib is metabolised predominantly by CYP3A4 (~76%). Minor contributions from several other CYPs and UGT1A4 were estimated at <25% in total. The active metabolite M5 (formed by CYP3A4) and the direct N-glucuronide conjugate, M11, (formed by UGT1A4) are the two major circulating metabolites identified.

Pharmacokinetics of metabolites

The oxidative metabolite M5 is pharmacologically active and is believed by the Applicant to make a meaningful contribution to the clinical efficacy of entrectinib.

An effective half-life of 19-35 hours was estimated in the 600 mg F2A group when one outlier was removed. In the DDI study with itraconazole and rifampcin (RXDX-101-12) where a single dose of entrectinib was administered in the formulation F06, the exposure ratio between M5 and entrectinib was around 0.3, but decreased both with itraconazole and with rifampicin. In the mass-balance study the average ratio between M5 and entrectinib was 0.36.

Bioequivalence

Different formulations of entrectinib were used in clinical studies, the first one was the F1 formulation. This formulation was used in ALKA-372-001 study as well as in the other studies conducted in patients (RXDX-101-01, RXDX-101-02 and RXDX-101-03) and in healthy subjects (CA14707 and RXDX-101-06).

F2 formulation was used only in study CA14707, whereas formulation F2A was used in several studies, among which RXDX-101-01 and RXDX-101-02. F2B was used only in CA14707 and RXDX-101-03 studies. Formulation F06 was developed as commercial formulation.

The applicant concluded that data support that comparative bioavailability linkage has been established between the three principal clinical research capsule formulations (F1, F2A, and F06).

F1 vs other formulations

Formulation F1 was compared with F2A and F2B in parallel in Study CA14707. In this study F1 was used in fed/fasted conditions and always with PPI, whereas F2A and F2B were used in fed/fasted conditions with/without PPI.

In fasted state with PPI, entrectinib exposure of F2A and F2B formulations were higher than the F1 capsule (AUCinf ratio: 1.92 and 4.09 for F2A and F2B, respectively). In fed state with PPI, the entrectinib exposure with F1 and F2A/F2B were essentially similar (AUCinf ratio: 1.08 and 1.11, respectively), however the formulations do not met the criteria for bioequivalence, because in each case the 90% CI of the difference between treatment means lay outside the range 80–125% for one or more comparisons.

No formal bioequivalence study was performed comparing formulations F1 and F2A in the fed state without PPI.

However, a comparison was performed in study RXDX-101-01 in adult patients in the fed state and plasma exposure of entrectinib was higher following administration of the F2A formulation compared to the F1 formulation. On day 1 AUCinf ratio was 1.43 (90% CI 1.09-1.85) and on day 14 AUCinf ratio was 1.09 (90% CI 0.70-1.72).

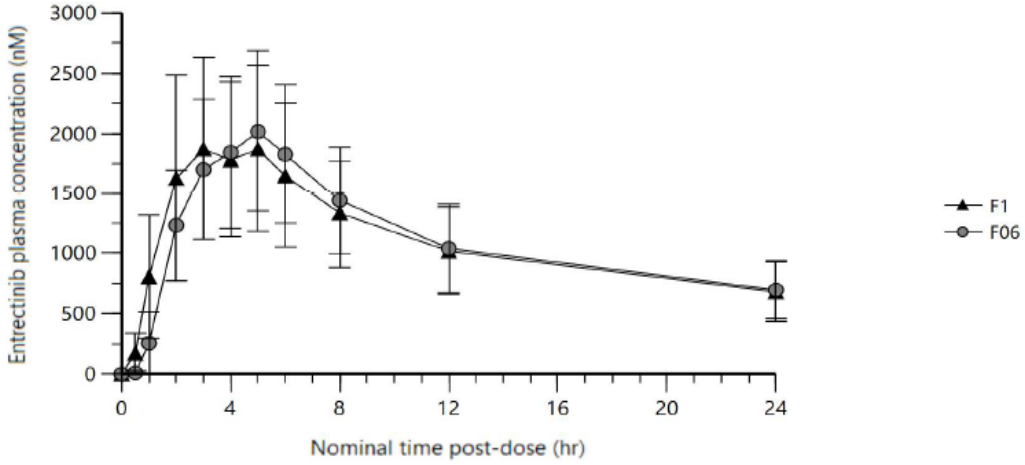
In RXDX-101-01 patients could take PPI or other agents impacting gastric pH, however their administration was not standardised and therefore the possible impact of these drugs on entrectinib exposure, especially in patients taken F1, could not be fully evaluated.

The only study in which F1 was used in fed condition and without PPI was RXDX-101-06 (relative BA of entrectinib administered as a granule formulation versus a capsule formulation in healthy adult male). If compared, the exposure of F1 formulation in fed condition (with PPI) reached in study CA14707 (Cmax 2250 nM, AUCinf 88600 nM.h) and those reached in RXDX-101-06 (Cmax 2990 nM, AUCinf 70100 nM.h) seems to be comparable. However, the F1 formulation is clearly not bioequivalent to no other formulation.

F06 vs other formulations

The bioequivalence between formulations F06 (200 mg) and F2A (200 mg) was evaluated in Study RXDX-101-15, a phase I, 2-part, 2 –way crossover study, open-label. In Part 1 subjects were randomized to receive 600 mg of entrectinib F06 or F2A formulation in fasted state. A wash-out period of at least 9 days occurred between entrectinib doses. The PK parameters Cmax, AUClast and AUCinf were within the acceptance criteria (IC 90%: 80-125%) and can be concluded that the two formulations are bioequivalent.

The Applicant conducted a relative bioavailability study (GP41048) comparing F1 and F06 capsule formulations in fed condition (after a light meal).



Arithmetic means (±SD)

Figure 3: Mean Entrectinib Plasma Concentration vs. Time Profiles from F1 and F06 Capsule Formulations following a Single 600 mg Dose of Entrectinib with a Light Meal (Study GP41048)

Table 14: **Summary of Derived Entrectinib Pharmacokinetic Parameters from F1 and F06 Capsule Formulations Following a Single 600 mg Dose of Entrectinib with a Light Meal (Study GP41048)**

Parameter	F1 (n = 14)	F06 (n = 14)	Ratio between treatment means (90% CI)
T_{lag} (hr)	0.0 (0.0-0.5)	0.5 (0.0-0.5)	
C_{max} (nM)	1865 (49%)	2003 (38%)	0.93 (0.82, 1.06)
T_{max} (hr)	4.0 (2.0-6.0)	5.0 (2.0-6.0)	

AUC_{last} (nM.hr)	41837 (51%)	42803 (48%)	0.98 (0.88, 1.08)
AUC_{inf} (nM.hr)	44643 (52%)	45639 (50%)	0.98 (0.89, 1.08)
Half-life (hr)	24.6 (14%)	24.5 (15%)	

AUC_{inf} = area under the curve to infinity; AUC_{last} = area under the curve from the time of dosing to the last measurable concentration; C_{max} = maximum concentration; T_{lag} = absorption lag-time; T_{max} = time of maximum concentration observed.
Geometric means (CV%) for C_{max}, AUC_{last}, AUC_{inf} and half-life; median (min-max) for T_{lag} and T_{max}.

In November 2019 the Applicant informed that an alternative drug substance polymorph (Form C) was selected as the final solid form for commercial and clinical use. In support to this change and in addition to all information provided in the quality section, a relative bioavailability of the F06 capsule formulation containing two drug substance polymorphs (either Form A or Form C) was investigated in Study GP41049. The study material (Reference: 200 mg-F06 capsules using Form A, and Test: 200 mg-F06 capsules using Form C) was produced at commercial-scale at the commercial drug product manufacturing site.

Study GP41049 was a randomized, open-label, two-treatment, two-period, two-way crossover study to demonstrate bioequivalence between entrectinib polymorph Forms A and C administered under fasted conditions in healthy male and female subjects. In each treatment period, subjects received a single 200-mg oral dose of entrectinib while fasted. Doses of entrectinib were separated by a washout period of 15 days.

Entrectinib pharmacokinetics were comparable between Form A and Form C F06 capsule formulations following administration of a single 200-mg entrectinib dose in fasting condition. The plasma concentration versus time profiles as well as the peak and total exposure parameters were similar between the two polymorphs. While entrectinib exposures were approximately 10% lower on average from Form C than Form A (Geometric LS mean ratio for Cmax, AUC0-t and AUC inf were 0.9123, 0.8954 and 0.9015, respectively), the 90% CIs of the ratio between treatment means lay within the range 80% to 125% for Cmax (CI: 0.8088, 1.0291), AUC0-t (CI: 0.8005, 1.0014), and AUC0-∞ (CI: 0.8070, 1.0069) and thereby met the standard criteria for bioequivalence. Entrectinib exposures in Period 1 were lower on average than corresponding exposures in Period 2, which was reflected as a statistically significant period effect in analyses of AUC0-∞ and AUC0-t (e.g., AUC0-∞ was approximately 23% lower on average in Period 1 than Period 2).

Overall variability was similar for both formulations, with geometric CV% for AUCs and Cmax ranging from 30.7% to 39.4% and 28.9% to 35.6%, respectively. Within-subject variability was also similar, with geometric CV% for AUCs and Cmax from 24.6% to 24.9% and 26.9%, respectively.

Entrectinib exposures following single 200-mg oral doses of Forms A and C in the fasted state were comparable while M5 exposure was approximately 15% lower for Form C than Form A.

Effect of PPI

The effect of lansoprazole under fasting conditions on entrectinib F06 formulation was assessed in Study RXDX-101-09, an open-label, randomized, 2-period, single-dose study. On day 1 of treatment A, a single oral dose of 600 mg entrectinib was administered under fasted conditions alone. During treatment B, lansoprazole was administered once daily for 9 consecutive days (days 1 to 9) with a single oral dose of entrectinib co-administered on day 5. A washout of at least 10 days occurred between entrectinib doses in each period.

The statistical assessments showed that entrectinib C_{max}, AUC_{last}, and AUC_{INF} were approximately decreased by 23%, 25% and 25%, respectively, when entrectinib was coadministered with lansoprazole compared to entrectinib alone.

Effect of food

The effect of food was evaluated in presence of PPI co-administration (study CA14707) for the F1 formulation and the plasma exposure was 321% higher in the fed state compared to the fasted state.

The effect of food was evaluated for the F2A formulation (without concomitant PPI administration) in studies CA14707 and RXDX-101-04 and the food effect was minor with a 32% and 17%-21% higher AUC in the fed state in the two studies, respectively.

The effect of high-fat meal, high-calories meal on entrectinib PK formulation F06 (600 mg dose) was evaluated in Study RXDX-101-15 (Part 2). The study was a 2-way crossover study and the washout period between the two period was 9 days. Following a single oral dose of 600 mg entrectinib F06 in Part 2, administration under the fasted condition and fed condition exhibited similar exposure profiles and entrectinib was readily absorbed with detectable entrectinib at 0.5 hour postdose. A median Tmax of 4 hours in the fasted state and 5 hours in the fed state was observed. Cmax, AUClast and AUCinf showed that food had no impact on entrectinib F06 exposure with the geometric mean ratio and 90% CI bound of GMR within 80-125% when entrectinib F06 was administered in a fasted state and following a high-fat, high-calories meal.

Dose proportionality and time dependencies

- **Dose proportionality**

Dose-proportionality was assessed in the two dose-escalation studies ALKA-372-001 and STARTRK-1 (F1 formulation). In ALKA study the dose proportionality was assessed for the doses ranging from 100 mg/m2 to 1600 mg/m2, administered in fasted state, and results indicate that the increase of exposure is not dose-proportional. The dose-proportionality assessment was performed on the dose level based on BSA and not on the actual dose administered to the patients, therefore patients included in the same cohort were administered with different doses.

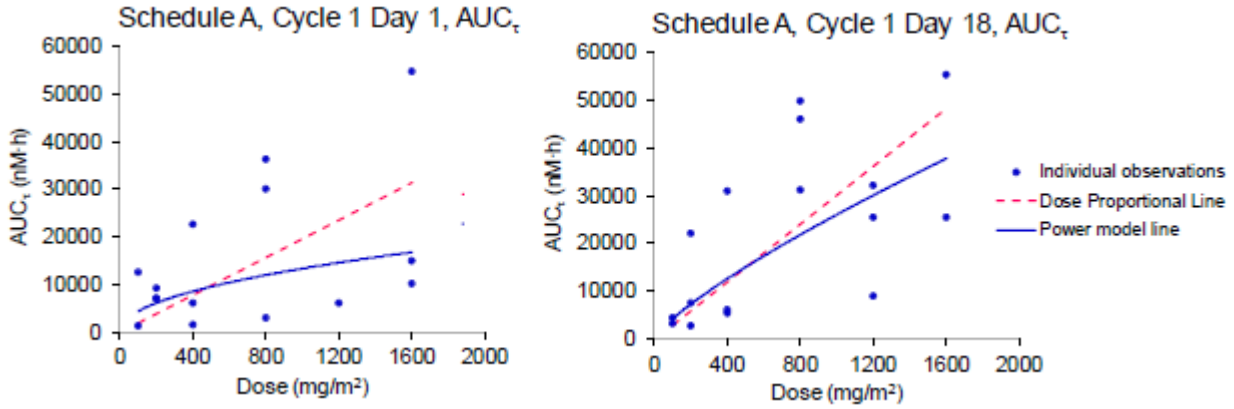


Figure 4: Dose proportionality assessment plot of AUCτ on Cycle 1 Day 1 and Day 18 in schedule A

In STARTRK-1 subjects included in the dose level 1 (100 mg/m2) were administered with an actual dose of 200 mg; subjects in Dose level 2 (200 mg/m2) were administered with 300 mg, 350 mg and 400 mg and those in the dose level 3 (400 mg/m2) were administered with 650 mg, 700 mg, 750 mg, 800 mg and 900 mg (excluding three patients in which a modification of dose was necessary and therefore were not included in the dose proportionality assessment). The dose proportionality statistical assessment after single and multiple dose was performed on the basis of actual dose administered to the patients. Results from power model indicate that no conclusion can be drawn on the dose-proportionality as the confidence intervals fell outside of the established acceptable bounds due to observed exposure variability.

Table 15: Statistical assessment of dose proportionality of entrectinib (F1 formulation)

Day	Dose Range	Parameter	β	β 90% CI (lower)	β 90% CI (upper)
1	100 – 400 mg/m² (BSA-Based) [b]	C_{max}	1.13	0.835	1.43
		AUC_{0-24}	1.19	0.868	1.51
	200 – 900 mg [a,c] (actual dose) [c]	C_{max}	1.24	0.992	1.48
		AUC_{0-24}	1.23	0.950	1.50
14	100 – 400 mg/m² (BSA-Based) [b]	C_{max}	1.01	0.554	1.47
		AUC_{0-24}	1.06	0.533	1.58
	200 – 800 mg (actual dose) [b]	C_{max}	1.05	0.710	1.40
		AUC_{0-24}	1.09	0.693	1.50

[a]One patient in 400 mg/m² dose group received a 900 mg dose based on BSA, but did not have PK data available for assessment on Cycle 1 Day 14
[b]Dose proportionality is concluded when 90% CI is entirely within the critical interval 0.839–1.16. If 90% CI of β is partially within this interval, dose proportional cannot be concluded (inclusive). If 90% CI of β lies entirely out of this interval, the conclusion would be not dose proportional.
[c]Dose proportionality is concluded when 90% CI is entirely within the critical interval 0.852–1.15. If 90% CI of β is partially within this interval, dose proportional cannot be concluded (inclusive). If 90% CI of β lies entirely out of this interval, the conclusion would be not dose proportional.

Since data on exposure were pooled based on the dose level and not on the actual dose administered, the Applicant was asked to provide details on the individual exposure in terms of AUC and Cmax based on the actual dose administered and further discuss/justify the range of dose linearity reported in the SmPC.

In order to better illustrate dose proportionality across the 100 mg to 800 mg dose range, data from all 10 completed healthy volunteer clinical pharmacology studies using F1, F2A and F06 formulations were pooled and a power model approach was used to assess the dose-proportionality. It was concluded that exposures were dose proportional across the dose range studied if the 90% confidence interval (CI) for was within the critical interval of [1ln(0.8)/ln(r), 1ln(1.25)/ln(r)], where r is dose ratio of highest dose to lowest dose. Nonproportionality was concluded if the 90% CI for lay entirely outside this interval, while 90% CI for partially within this interval was considered inconclusive.

Statistical analyses demonstrated that exposures (pooled data) met specified criteria for dose proportionality under both fed and fasted conditions: the estimated power model slope parameter (beta) for AUCinf was close to 1.0 and the corresponding 90% confidence intervals (CI) fell within the defined critical intervals. Similar results were achieved when data were split by formulation. Although the F1 formulation was only tested at 600 mg, the F2A and F06 formulations were both tested at three separate doses (F2A: 400 mg, 600 mg, and 800 mg; F06: 100 mg, 200v, and 600 mg). Statistical analyses confirmed that exposures from the F06 formulation across the dose range 100 mg to 600 mg met specified criteria for dose proportionality under fasted conditions as the estimated beta values for AUC_{inf} and C_{max} were close to 1.0 and the corresponding 90% CIs fell within the defined critical interval.

Table 16: Summary of statistical analysis of dose proportionality of F2A and F06 formulations

Formulation	Parameter	Food Status	ln(alpha)	Beta	Dose Range	Beta Equivalence Criterion Limits
F2A	AUC_{inf}	Fasted	5.95 (4.67, 7.22)	0.76 (0.57, 0.96)	400800	0.68, 1.32
		Fed	1.84 (-2.21, 5.89)	1.41 (0.79, 2.04)	600800	0.22, 1.78
	C_{max}	Fasted	3.70 (2.68, 4.73)	0.63 (0.47, 0.79)	400800	0.68, 1.32
		Fed	4.41 (1.70, 7.12)	0.51 (0.09, 0.93)	600800	0.22, 1.78
F06	AUC_{inf}	Fasted	4.39 (3.84, 4.94)	1.01 (0.92, 1.10)	100600	0.88, 1.12
		Fed	NA	NA	600	NA
	C_{max}	Fasted	1.51 (1.07, 1.95)	0.97 (0.90, 1.04)	100600	0.88, 1.12
		Fed	NA	NA	600	NA

Abbreviations: NAnot applicable.

- **Time dependency**

The time-dependency was evaluated in the STARTRK-1 study and the $AUC_{0\text{-}24h}$ was estimated both on day 1 and on day 14.

Table 17: STARTRK-1: Summary of Geo. Mean (geoCV%) PK Parameters for Entrectinib and M5 by Dose Group Following a Multiple Ascending Dose of Entrectinib (Fed; Cycle 1 Day 14)

		Entrectinib			M5			
Dose Group	N	C_{max} (nM)	$AUC_{0\text{-}24}$ (nM • h)	R_{acc} $AUC_{0\text{-}24}$	C_{max} (nM)	$AUC_{0\text{-}24}$ (nM • h)	R_{acc} $AUC_{0\text{-}24}$	M/P $AUC_{0\text{-}24}$ ratio
100 mg/m² F1	4	1040 (50.4)	16800 (66.0)	2.08 (44.1)	680[g] (402, 1150)	12600[g] (8310, 19000)	3.96[g] (2.74, 5.72)	0.549[g] (0.282, 1.07)
200 mg/m² F1	5	1530 (79.5)	22500[a] (96.8)	1.15[a] (77.6)	713 (42.9)	12800[a] (60.4)	1.80[a] (25.7)	0.569[a] (44.6)
400 mg/m² F1	7	4030 (60.4)	68500 (65.3)	1.58[b] (23.7)	892[j] (36.9)	16400[j] (37.2)	1.46[f] (78.9)	0.273[j] (39.1)
800 mg F1	6	4720 (53.3)	77300[b] (72.7)	1.57[b] (23.0)	2910 (65.3)	49600[b] (62.1)	2.59[b] (25.8)	0.642[b] (61.6)
600 mg - 800 mg by BSA F1	3	3030 (27.3)	50200 (24.7)	1.16 (30.0)	845 (89.0)	14400 (96.2)	1.89[g] (1.96, 1.82)	0.286 (63.1)
600 mg F1	17	2740 (58.1)	43900[c] (63.9)	2.11[c] (35.2)	634 (76.4)	11600[h] (75.5)	2.02[i] (77.4)	0.265[c] (65.6)
600 mg F2A	12	3130 (80.3)	48000[d] (76.5)	1.55[e] (49.1)	1250 (89.6)	24000[d] (97.4)	2.84[e] (93.1)	0.499[d] (142)

In Study STARKTRK-2 entrectinib was administered orally on a continous daily dosing regimen at a dose of 600 mg once-daily in reapeted 4-week cycles. The mean accumulation ratio was 1.91 for entrectinib and 2.02 for M5, in line with the half-life of about 20 hours for entrectinib and 40 hours for M5. The popPK model estimated that the accumulation ratio for entrectinib (600 mg QD) and M5 is 1.89 and 2.01, respectively.

Special populations

- **Impaired renal function**

No dedicated study has been performed in subjects with impaired renal function.

In clinical studies STARTRK-1, STARTRK-2, and STARTRK-NG 43% of enrolled patients (120 out of 276) had mild to moderate impairment, while no severe renal impaired subjects have been enrolled.

In the population PK report to confirm the absence of a clinically important difference in PK among patients with renal dysfunction, entrectinib and M5 exposures have been compared between patients with mild to moderate renal impairment and all other patients with normal renal function.

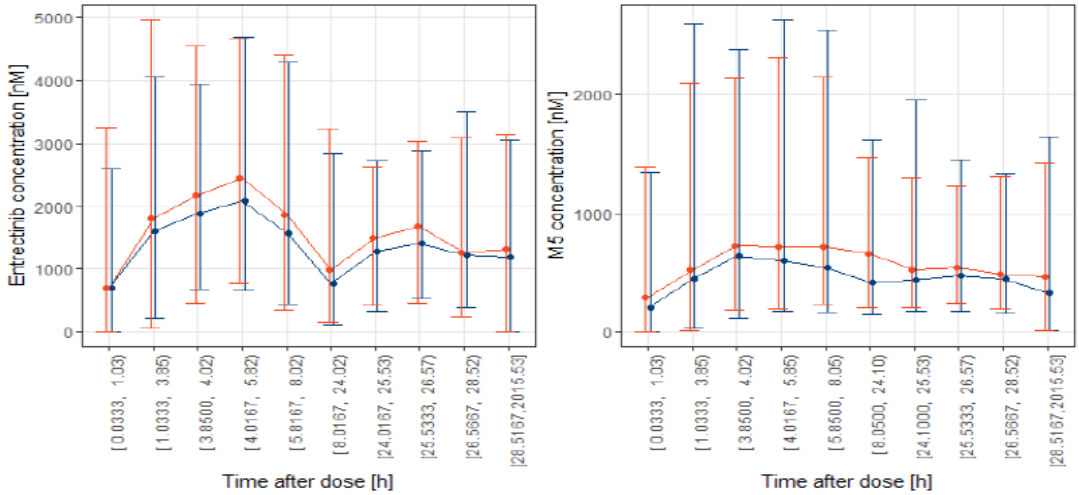


Figure 5: Median (5th and 95th percentiles) exposure in mild or moderate renal impaired patients (orange) vs. non-impaired patients (blue)

High variability in systemic exposure was observed in both groups, but there were no clear differences between groups.

- **Impaired hepatic function**

No dedicated study has been performed in subjects with impaired hepatic function.

In clinical studies STARTRK-1, STARTRK-2, and STARTRK-NG 20% of enrolled patients (57 out of 276) had mild to moderate impairment, and only 1 patient (0,3%) had severe impairment.

In the population PK the effects of hepatic impairment through comparison of entrectinib and M5 exposure between groups of patients with different levels of hepatic function was explored.

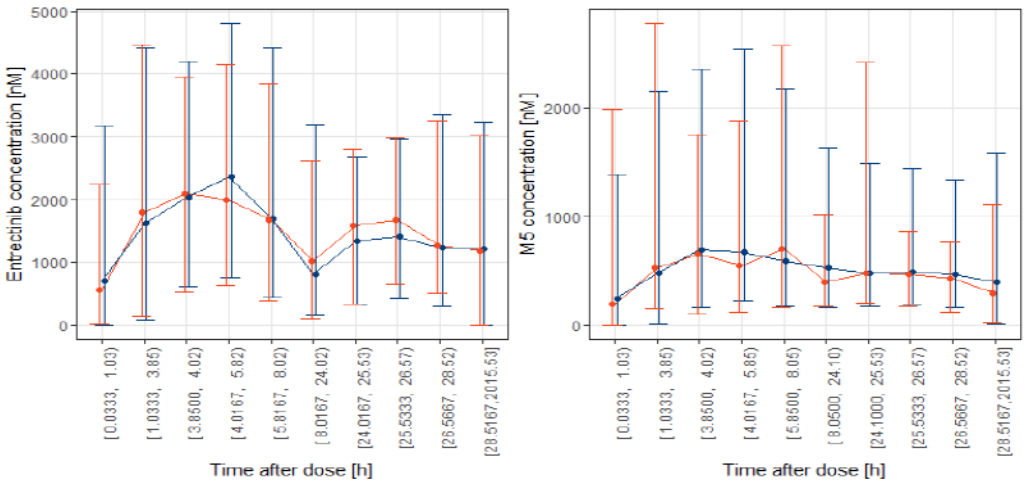


Figure 6: Median (5th and 95th percentiles) exposure in mild or moderate or severe hepatic impaired patients (orange) vs. non-impaired patients (blue)

- **Gender**

The influence of sex was not formally investigated in the population pharmacokinetic model, but illustrated by displaying the distribution of individual ETA for each parameter across age and sex (e.g. using box-and-whisker plots or equivalent). Visually a correlation does not appear apparent.

- **Race**

In study RXDX-101-04, both Japanese and Caucasian subjects were included, and the PK data was similar between the groups. Only 5 subjects included in the population pharmacokinetic analysis were Asian-Japanese, therefore, the influence of race was not assessed formally.

- **Weight**

Weight was found to influence the PK parameters in the population pharmacokinetic model. Weight was allometrically scaled with fixed exponents of 0.75 and 1 for clearance and distribution parameters.

A flat dose of 600mg (using F2A formulation in fed state) was assumed to be administered to subjects with different body weights. A total of 500 patients were simulated for each category of the body weight and the predicted AUCss on Day 14 (steady state) was computed.

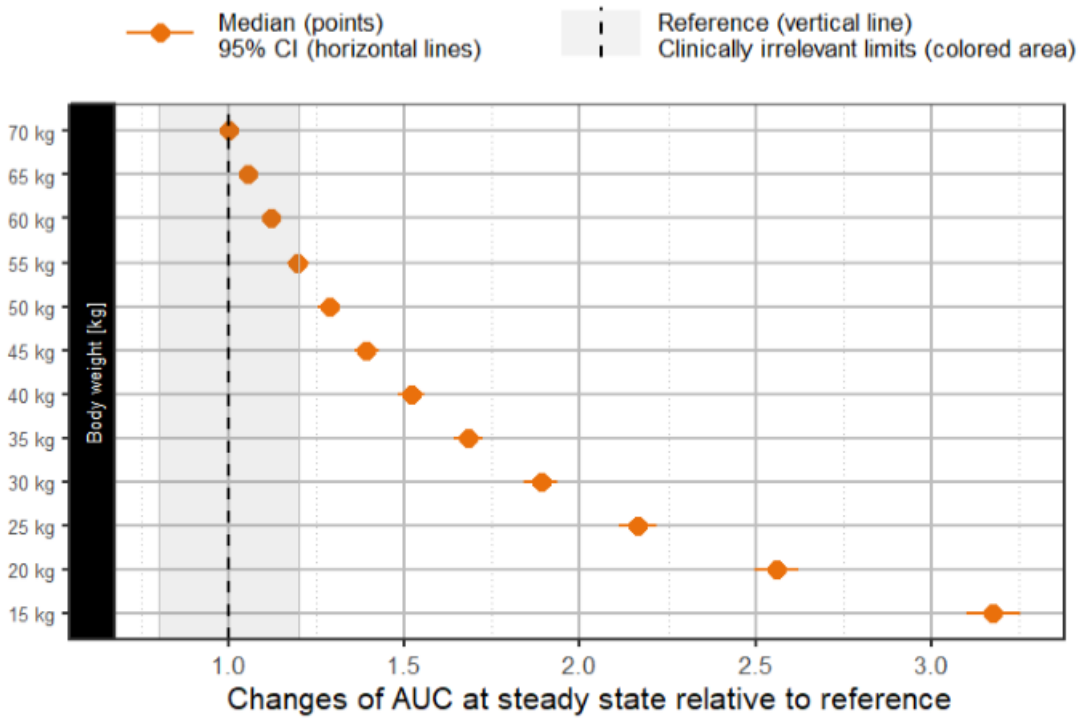


Figure 7: Predicted AUC at steady-state for each category of body weight

- **Elderly**

There have been no dedicated studies in elderly individuals, and the effects of age on entrectinib PK were not specifically tested in the clinical pharmacology program or in the population pharmacokinetic analysis. Age was graphically assessed (ETA plotted against age) in the PopPK analyses, and no differences were observed.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	59	15	1

- **Paediatric population**

The effect of entrectinib is being evaluated in children, adolescents and young adult patients in Study STARTRK-NG. This is a 5-part, Phase I/Ib multicenter, open-label dose escalation and expansion study in which Part A of the study was a dose escalation in patients with relapsed or refractory extracranial solid tumors, with or without molecular alterations, to determine the MTD or RP2D, PK, and safety profile of entrectinib. At the time of the clinical data cut-off (31-May-2018), only data from the Part A (16 subjects) were included in the analysis set. In Part A, all patients received entrectinib administered orally with F1, with food, QD, in repeated 4-week (28-day) cycles. The BSA-based dose levels were 250, 400, 550, and 750 mg/m^2, according to a dosing nomogram. While the other patients in Part A received entrectinib with formulation F1, 3 patients received entrectinib with the formulation F2B. The dose of 550 mg/m^2 was defined as the MTD in this study. The Applicant performed a comparison between exposure reached with 550 mg/m^2 in paediatrics and 600 mg flat dose in adults from STARTRK-1. The exposures were comparable when taking into account the difference in BSA-dosing between pediatrics and adults (~1.8). Based on this exploratory assessment, the assumed

recommended dose in children was 300 mg/m^2. Simulation exercises were performed to predict the dose (using F2A formulation) for the paediatric population matching the adult exposure. PopPK has been used with application of theory-based allometric scaling. The estimated dose of 300mg/m^2 led to a similar predicted systemic exposure in paediatric patients compared with the predicted exposure in adult patients following 600 mg flat dose once daily. However, given that PK data is pivotal to support dosing in children, the Applicant was asked to improve the model in order to better understand the factor describing a different bioavailability observed in children and adults (and not related to formulation).

Updated parameters estimates of the popPK model were submitted after including data from 13 additional paediatric patients comprising 452 additional entrectinib and M5 observations.

The PopPK estimates of the best model and the updated model are presented in **Table 18**

Table 18: Parameter Estimates for the Best-Updated PK Model for Entrectinib and M5 Without and with Additional Paediatric data

Parameter	Unit	[3]Estimate best model (%RSE)	[4]Estimate best-updated model (%RSE)
Fixed effect			
CL/F	[L/h/70kg]	19.6 (2.8)	19.6 (2.8)
V/F	[L/70kg]	551 (3.4)	554 (3.4)
KA	[1/h]	1.01 (8.3)	1.07 (6.1)
D1	[h]	1.35 (9.9)	1.31 (8.9)
Frel	-	1.00 FIX	1.00 FIX
CLM/F	[L/h/70kg]	52.4 (3.8)	52.0 (3.7)
VM/F	[L/70kg]	81.1 (8.2)	82.9 (7.5)
Random effect BPV			
CL/F	[CV%]	30.8[2] (11.2)	31.1[2] (11.3)
KA	[CV%]	122[2] (12.0)	128[2] (11.8)
Frel	[CV%]	40.1[2] (10.6)	40.6[2] (9.9)
CLM/F	[CV%]	54.6[2] (11.6)	53.9[2] (11.2)
RV additive	[CV%]	131[2] (19.2)	126[2] (17.6)
Covariate effect			
Effect of WT on CL/F and CLM/F	-	0.75 FIX[1]	0.75 FIX[1]
Effect of WT on V/F and VM/F	-	1 FIX[1]	1 FIX[1]
Effect of formulation F1 on Frel in study RXDX-101-03	-	0.718 (10.8)	0.644 (9.2)
Error model			
Additive (entrectinib)	[nM]	108 (16.7)	113 (13.5)
Proportional (entrectinib)	[%]	29.3 (4.3)	29.7 (3.2)
Additive (M5)	[nM]	34.7 (13.4)	31.9 (15.9)
Proportional (M5)	[%]	32.1 (4.0)	33.4 (4.1)
OFV	-	91597.8	97488.4
Number of cancer patients	-	276	289
Number of observations	-	7243	7695

BPV=between-patient variability; CV=coefficient of variation; OFV=objective function value; WT=body weight; RV=residual variability; RSE=relative standard error; L=liter; h=hour; kg=kilogram; nM=nanomolar; %=percentage.
[1]Allometric coefficients: fixed.
[2]Computed as the squared root of the omega.
[3]Parameters estimated best model.
[4]Parameters estimated best-updated model (including 13 additional pediatric patients).

Simulated exposures in adults and in adolescents of a relevant weight and BSA were submitted in order to show a matching with those obtained in adults (a range that encompasses 90% of the adults when given 600 mg entrectinib). Simulations were performed using the recommended doses of 400 mg and 600 mg for BSA Categories IV and V, respectively in adolescents (see section 4.2 of the SmPC).

The simulations are based on the Center for Control and Prevention (CDC) database. Although the typical values of BSA in adolescents (≥ 12 years) ranged from 1.3 m2 to 1.5 m2, in order to cover the lower boundary of Category IV (1.11 m2 BSA) the age range between 10 and 11 years old had to be included for the purpose of the simulations that were performed by 4 kg increment body weight (from 30 to 62 kg) and by age (from 10 to 18 years). The simulated exposure in adolescents was compared to the exposure in adults treated with 600 mg and for all doses it is within the 5th and 95th percentile of exposure in adults (shade area, see figures below).

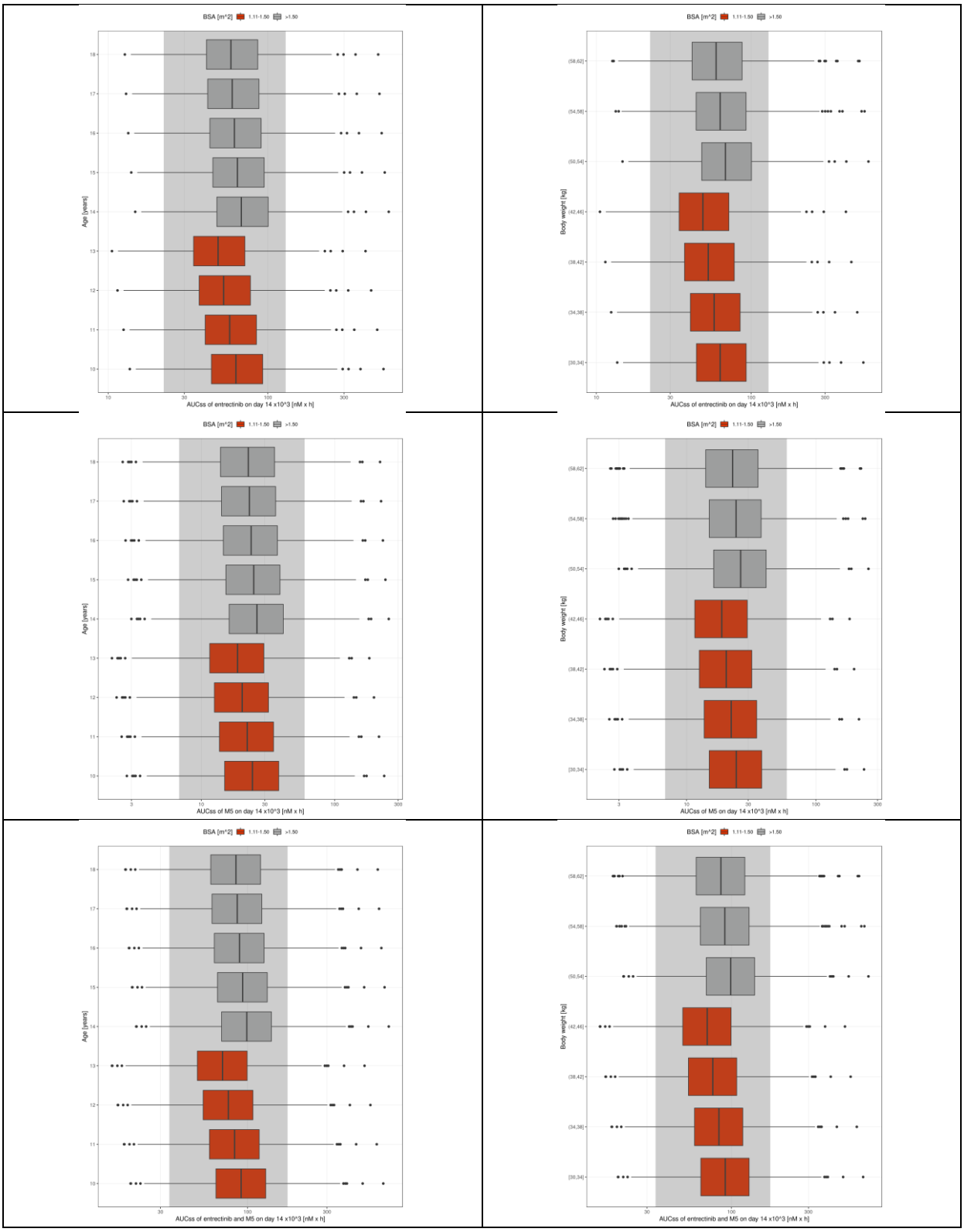


Figure 8: Predicted AUCss (x103 nM.h) of entrectinib (top panels), of M5 (middle panels), and sum of entrectinib and M5 (bottom panels) in adolescents ≥12y – stratified either by age (left panels, with 1000 simulated patient in each age group) or by 4 kg increment of body weight (right panels) – recommended dose per the SmPC (i.e. 400 mg QD for Cat. IV and 600 mg QD for Cat. V) – grey area represent the 5th and 95th percentiles in adults following 600 mg QD

Pharmacokinetic interaction studies

Entrectinib and M5 as perpetrators for DDI

The *in vitro* studies showed that entrectinib did not reversibly inhibit the metabolism catalysed by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 (using midazolam as the probe substrate) at the higher concentration tested. Entrectinib inhibited the activity of CYP3A4, using testosterone as the probe substrate, with an IC50 value of 2.04 µM. Value close to those reached with recommended dose (1.99 µM).

Considering that entrectinib inhibits *in vitro* the activity of CYP3A4 with an IC50 value close to the Cmax value reached with the clinically relevant dose, the DDI with a CYP3A substrate (midazolam) was evaluated in a clinical study RXDX-101-14 as well as by PBPK modelling.

Results from RXDX-101-14 study confirm *in vivo* the inhibitory effect of entrectinib on CYP3A4 with an increase of midazolam AUCinf by 50% after multiple dose.

The inductive potential of entrectinib on CYP enzymes (1A2, 2C8, 2C9, 3A4) was evaluated in *in vitro* Study 1087289 and showed that treatment of cultured human hepatocytes with up to 10 µM of entrectinib did not induce CYP1A2, CYP2C19 or CYP3A4/5 enzyme activity, while entrectinib induced concentration dependent increases in CYP2C8, CYP2C9 and CYP3A4 mRNA expression level, with a significant increases observed mainly at entrectinib concentration of 10 µM.

Entrectinib (0.1, 0.3, 1, 3, and 5 µM) was newly examined for its potential to induce CYP2B6 in primary cryopreserved human hepatocytes among three separate donors (1095573). The experiments appear to be of acceptable quality, and at the cut-off concentration 1.9 uM (50xCmax), no increase in mRNA (>2 times) was observed. The data can be used to exclude a risk for clinical induction of CYP2B6.

The potential of entrectinib to induce CY3A4 was further evaluated by *in vivo* DDI study RXDX-101-14 using midazolam (see above) as substrate as well as by PBPK modelling.

Entrectinib exhibits inhibitory potential towards Pg-p and BCRP, with IC50 value close to clinically relevant concentration. The effect of entrectinib (F2A formulation) as inhibitor of P-gp substrate was further evaluated *in vivo* in a clinical study using Digoxin as probe drug (study RXDX-101-13). Results indicates that entrectinib is a weak Pgp inhibitor. The digoxin Cmax, AUClast, and AUCINF were approximately 28%, 19%, and 18% higher when digoxin was coadministered with entrectinib than digoxin alone, respectively, confirming that entrectinib is an *in vivo* inhibitor of Pgp.

The ability of entrectinib (0.03, 0.1, 0.3, 1, 3, 10 and 30 µM) to inhibit human uptake transporters, namely, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3) was evaluated by measuring the accumulation of probe substrates (estradiol-17β-glucuronide [OATP1B1 and OATP1B3], metformin [OCT2], p-aminohippurate [OAT1] or estrone-3-sulfate [OAT3]) in transporter-expressing and control HEK293 cells in the presence of entrectinib.

In the presence of entrectinib (0.3 to 30 µM) the transporter-dependent uptake rate of estradiol-17β-glucuronide into OATP1B1-expressing cells was reduced from 1.71 to 0.274 pmol/mg/min (84% inhibition). The calculated IC50 is 6.46 µM. The inhibitory potential of entrectinib against OATP1B1 was further evaluated in in vitro study 1090527. The results showed that entrectinib inhibits OATP1B1b

with IC50 values of 3.89 µM and 4.22 µM, when using rosuvastatin and pitavastatin, respectively. For OATP1B1, in vivo inhibition by entrectinib cannot be excluded as the in vitro IC50 values is lower than the cut-off used for evaluation of interaction potential *in vivo*.

In *in vitro* study 1087486, Entrectinib was investigated over the concentration range of 0.1 – 30 µM for its inhibition potential against human OCT1, MATE1, MATE2-K, and BSEP mediated transport.

Entrectinib was shown *in vitro* to be an inhibitor of MATE1, MATE2-K and BSEP with IC50 values of 1.1, 19.4 and 13.3 µM, respectively. However, these IC50 values are similar or higher than the cut-off value relevant for renal transporters and no evaluation *in vivo* is necessary. Metabolite M5 directly inhibited every CYP enzyme examined, however the IC50 values were greater than the cut-off for the metabolite M5 (0.8 µM) and no evaluation of interaction potential *in vivo* is necessary.

Metabolite M5 was shown *in vitro* to be an inhibitor of MATE1, MATE2-K, BCRP and P-gp with IC50 values of 0.64, 3.14, 8.35 and 10.1 µM, respectively. However, these IC50 values are similar or higher than the cut-off value for M5 no evaluation *in vivo* is necessary. No inhibition was seen *in vitro* for M5 on OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 and BSEP.

Entrectinib and M5 as victim for DDI

Entrectinib is a P-gp substrate, but not a substrate of BCRP, OATP1B1 and OATP1B3.

In vivo study RXDX-101-12 was performed in order to assess the effect of inducer/inhibitor on entrectinib PK. Results showed that itraconazole increased entrectinib AUC_{inf} of 504% and C_{max} of 73%, whereas , the presence of rifampicin, decrease entrectinib AUCinf and Cmax of about 77% and 56%, respectively (see section 4.5 of the SmPC).

M5 does not appear to be a clinically relevant substrate for human OCT1, OATP1B1 or OATP1B3, while M5 is likely a substrate for BCRP and P-gp. The metabolite M5 was also shown to be a substrate of CYP3A4.

Systemic hormonal contraceptives

There are no data available on the potential effect of entrectinib on systemic hormonal contraceptives.

2.4.3. Pharmacodynamics

Mechanism of action

No dedicated clinical studies investigating the mechanism of action were submitted.

Entrectinib is a potent inhibitor of 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; encoded by the gene ROS1), and anaplastic lymphoma kinase (ALK; encoded by the gene ALK). The major active metabolite of entrectinib, M5, showed similar *in vitro* potency and activity.

Primary and Secondary pharmacology

No dedicated clinical studies for primary pharmacology were submitted.

Exposure-efficacy relationship

An exposure/efficacy analysis was conducted including data from patients enrolled in studies STARTRK-1 and STARTRK-2. Data from ALKA study were not included in the popPK analysis due to the results of the cross-validation.

The analysis was run in two separate sub-groups of patients: ROS1-positive NSCLC patients and those with NTRK fusion-positive solid tumours. The AUCss was used as metric of exposure.

In ROS1 positive NSCLC patient analysis, a total of 39 patients were retained in the exposure tumour size analysis. 33 (85%) were categorised as partial responders and were allocated to the previously defined 5 categories of predicted AUCss: [13.4, 50.5), [50.5, 64.6), [64.6, 81.1), [81.1, 105.3), [105.3, 310.2] x103 nM*h. The proportion of PR patients was neither increasing nor decreasing monotonically going from the lower to the higher categories of exposure. Adding CR and PR patients, the responders rate was equal to 87.2% (34 patients out of 39), with an exact 95%CI ranging between 72.6% and 95.7%. The median DOR in responder ROS1+ NSCLC patients was equal to 338 days and the exploratory graphic provided indicate a trend to lower DOR with higher exposure in the studied range. The assessment of correlation between shrinkage rate (KS) and growth rate (KG) versus exposure (AUCss for both entrectinib and M5) was performed and showed a large inter-patient variability. The slope estimates for the linear model characterising the trend in KS and KG as function of log10(AUCss) were equal to 7.11 for log(KS) (with a 95%CI including 0 and ranging between -5.96 and 20.2) and 1.08 for log(KG) (with a 95%CI including 0 and ranging between -0.526 and 2.68).

Among NTRK fusion positive patient analysis, 27 (54%) patients were categorised as partial responders and were allocated to the previously defined 5 categories of predicted AUCss: [13.4, 50.5), [50.5, 64.6), [64.6, 81.1), [81.1, 105.3), [105.3, 310.2] x103 nM*h. The proportion of PR patients was neither increasing nor decreasing monotonically going from the lower to the higher categories of exposure. Adding CR and PR patients, the responders' rate was equal to 62% (31 patients out of 50), with an exact 95%CI ranging between 47.2% and 75.3%. The median DOR in responder NTRK fusion positive patients was equal to 217 days. And the exploratory graphic provided indicated no marked trend towards prolonged DOR with higher exposure in the studied range.

The assessment of correlation between KS and KG and exposure showed a large inter-patient variability. The slope estimates for the linear model characterising the trend in KS and KG as function of log10(AUCss) were equal to -5.69 for log(KS) (with a 95%CI including 0 and ranging between -17.2 and 5.84) and 0.412 for log(KG) (with a 95%CI including 0 and ranging between -2.09 and 2.91).

Exposure-safety relationship

An exposure-safety analysis was performed in order to evaluate the correlation between entrectinib concentration and QT prolongation. This relationship was evaluated using a linear mixed-effects model on the basis of data collected during Study RXDX-101-02, a phase II, single arm, open-label study in patients with solid tumors administered with 600 mg of entrectinib in a continuous daily dosing regimen in 4-week cycles. Since no placebo arm was foreseen in the study, the baseline QTcF values were used in the model. Goodness-of-fit plots were submitted, among which those referred to model predicted versus observed ΔQTcF.

Logistic regressions were used to investigate the exposure-AE relationships in order to ascertain whether the occurrence of safety events could be attributed to the variability in entrectinib and M5 exposure in patients from studies STARTRK-1, STARTRK-2, and STARTRK-NG. The dose range investigated in the analyses was from 200 mg/m2 to 400 mg/m2 BSA-dosing and 600 mg to 800 mg flat dose. Results from the logistic regression models indicated that a higher frequency of SAEs or of Grade≥3 AEs were observed at higher exposure. The relationship between AUC,ss and probability of occurrence of Grade≥3 AEs, and the relationship between Cmax,ss and probability of occurrence of SAEs, showed a higher statistical significance compared with other exposure measures.

2.4.4. Discussion on clinical pharmacology

Overall, the bioanalytical methods are conducted in line with the relevant Guideline on method validation.

The different formulations (F1, F2A, F2B and F06) were compared. Entrectinib exposure of F2A and F2B were higher than the F1 capsule in fasted state with PPI, whereas the exposure is similar in fed state with PPI, however the BE criteria were not met. No formal BE study was performed in order to compare the formulation F1 and F2A in the fed state without PPI. A bioequivalence study RXDX-101-15 in fasting condition was submitted to bridge the exposure of F06 formulation (200 mg) with F2A (200 mg) that is the formulation most used in clinical trials (as well as F1). The PK parameters Cmax, AUClast and AUCinf were within the acceptance criteria (IC 90%: 80-125%) and two formulations F2A and F06 can be considered bioequivalent.

A relative BE study compared F06 with F1 formulation in fed condition (light meal) and the two formulations reached a similar exposure.

A BE study (GP41049) was also conducted to compare F06 capsules formulation produced with active substance polymorph A (used in clinical trials) and the active substance polymorph C (selected as final solid form for commercial and clinical use). The study was conducted as requested by the relevant Guideline and the F06 capsules produced with the two polymorph resulted to be bioequivalent.

Entrectinib solubility is pH dependent, therefore the formulation F1 without acidulant in gelatin capsules results to be very sensitive to gastric pH. In order to reduce this sensitivity and therefore the variability in exposure due to the gastic pH, an acidulat was added to F2A and F2B as well as in F06.

The effect of high-fat meal on entrectinib PK formulation F06 (600 mg) was also evaluated and results showed that the exposure was not significantly altered by food, therefore entrectinib can be administered with and without food.

The Applicant submitted a statistical analysis of dose-proportionality for F06 formulations in fed and fasted conditions. The proportionality was demonstrated between 100 mg and 600 mg.

Entrectinib did not demonstrate to have a time-dependent exposure.

The Applicant submitted a statistical analysis of dose-proportionality for F06 formulations in fed and fasted conditions. Entrectinib has linear pharmacokinetics in the dose range of 100 mg to 600 mg.

The population PK model estimated mean accumulation at steady-state following 600 mg once daily administration of entrectinib was 1.89 (±0.381) and 2.01 (±0.437) for M5.

Entrectinib and its major active metabolite M5 are highly bound to human plasma proteins independent of drug concentrations. In human plasma, entrectinib and M5 had similar protein binding with >99% bound at a clinically relevant concentration.

Following administration of a single dose of [^{14}C]-labelled entrectinib, 83% radioactivity was excreted in faeces (36% of the dose as unchanged entrectinib and 22% as M5) with minimal excretion in urine (3%).

Entrectinib and M5 account for approximately 73% of radioactivity in systemic circulation at C_{max}, and approximately half of total radioactivity AUC_{INF}.

Inter-individual variability

Variability in entrectinib exposure is higher in patients compared to healthy volunteers, however, considering exposure from study RXDX-101-14 where patients received 600 mg entrectinib once daily

for 15 days (Days 8 to 22) using the F06 capsule formulation in a well-controlled study, the difference in CV% between healthy subjects and patients is more contained.

Special population

No differences in entrectinib exposure were noted in patients older than 65 years and younger adults based on pharmacokinetic analysis. No dose adjustment is required in patients ≥ 65 years of age.

Negligible amounts of entrectinib and the active metabolite M5 are excreted unchanged in urine (~3% of the dose) indicating that renal clearance plays a minor role in the elimination of entrectinib. Based on population pharmacokinetic analyses, the pharmacokinetics of entrectinib are not significantly affected in renal impairment. No dose adjustment is required in patients with mild or moderate renal impairment. The impact of severe renal impairment on the pharmacokinetics of entrectinib is unknown.

As elimination of entrectinib is predominantly through metabolism in the liver, hepatic impairment may increase the plasma concentration of entrectinib and/or its major active metabolite M5. Limited clinical data is available in patients with hepatic impairment.

No clinically significant differences in the pharmacokinetics of entrectinib were observed based on mild hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment. The impact of moderate to severe hepatic impairment on the pharmacokinetics of entrectinib is unknown. A dedicated study of the effects of hepatic impairment on entrectinib PK is planned to be completed by December 2021 (see RMP).

No clinically significant differences in the pharmacokinetics of entrectinib were observed based on age (4 years to 86 years), sex, race (Asian, Black and White) and body weight (32 kg to 130 kg) (see section 5.2 of the SmPC).

The proposed dosing regimen in children from 4 years old was not supported because of the lack of sound PK data supporting it. Given the uncertainties regarding the lower bioavailability in children, the popPK analysis was not considered adequate to inform dose regimen decision. In addition, no paediatric formulation is available.

Data obtained from population pharmacokinetic analyses show that in paediatric patients 12 years and older, a dose of 400 mg Rozlytrek once daily for BSA range 1.11 m^2 to 1.50 m^2, and a dose of 600 mg Rozlytrek once daily for BSA range ≥1.51 m^2 results in a similar systemic exposure attained in adults treated with 600 mg of Rozlytrek, once daily.

Initially the simulation of exposure (AUCss) of entrectinib and its metabolite, M5, was performed in subjects weighing ≥38 kg and aged ≥12 years of age. Thereafter additional simulations were provided for weight below 38 kg, including the ranges 30-34 kg and 34-38 kg that fall in the BSA category 1.1-1.5 m2 and representing adolescents of 12 years with lower percentiles of weight. The simulations performed for adolescents in this categories of weight (within BSA 1.1-1.5 m2) also showed that the exposure is within those obtained in adults.

Interactions

Entrectinib is a weak inhibitor of CYP3A4. Co-administration of entrectinib 600 mg once daily with oral midazolam (a sensitive CYP3A substrate) in patients increased the midazolam AUC by 50% but reduced midazolam C_{max} by 21%. Caution is advised when entrectinib is administered together with sensitive CYP3A4 substrates with a narrow therapeutic range (e.g., cisapride, cyclosporin, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil and sirolimus), due to the increased risk of adverse drug reactions.

In vitro data suggest that entrectinib has inhibitory potential towards P-glycoprotein (P-gp).

Co-administration of a single 600 mg dose of entrectinib with digoxin (a sensitive P-gp substrate) increased digoxin C_{max} by 28% and AUC by 18%. The renal clearance of digoxin was similar between treatments of digoxin alone and digoxin co-administered with entrectinib, indicating minimal effect of entrectinib on renal clearance of digoxin.

The effect of entrectinib on digoxin absorption is not considered clinically relevant, but it is unknown whether the effect of entrectinib may be larger on more sensitive oral P-gp substrates such as dabigatran etexilate.

Inhibition of BCRP was observed in *in vitro* studies. The clinical relevance of this inhibition is unknown, but caution is advised when sensitive oral BCRP substrates (e.g. methotrexate, mitoxantrone, topotecan, lapatinib) are co-administered with entrectinib, due to the risk of increased absorption.

In vitro data indicate that entrectinib has weak inhibitory potential towards OATP1B1. The clinical relevance of this inhibition is unknown, but caution is advised when sensitive oral OATP1B1 substrates (e.g. atorvastatin, pravastatin, rosuvastatin repaglinide, bosentan) are co-administered with entrectinib, due to the risk of increased absorption.

In vitro studies indicate that entrectinib may induce PXR regulated enzymes (e.g. CYP2C family and UGT). Co-administration of entrectinib with CYP2C8, CYP2C9 or CYP2C19 substrates (e.g. repaglinide, warfarin, tolbutamide or omeprazole) may decrease their exposure

It is currently unknown whether entrectinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives are advised to add a barrier method. This is particularly relevant considering the non-clinical findings (see sections 4.5, 4.6 and 5.3 of the SmPC).

Based on *in vitro* data, CYP3A4 is the predominant enzyme mediating the metabolism of entrectinib and formation of its major active metabolite M5.

Co-administration of multiple oral doses of rifampin, a strong CYP3A inducer, with a single oral dose of entrectinib reduced entrectinib AUC_{inf} by 77% and C_{max} by 56%.

Co-administration of entrectinib with CYP3A or P-gp inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's Wort -Hypericum perforatum) should be avoided.

Co-administration of itraconazole, a strong CYP3A4 inhibitor, with a single oral dose of entrectinib increased AUC_{inf} by 600% and C_{max} by 173% which could increase the frequency or severity of adverse reactions.

Co-administration of strong and moderate CYP3A or P-gp inhibitors (including, but not limited to, ritonavir, saquinavir, ketoconazole, itraconazole, voriconazole, posaconazole, grapefruit or Seville oranges) should be avoided. If concurrent use of strong or moderate inhibitors is unavoidable in adult patients, administration of entrectinib should be limited to 14 days and the dose should be reduced to 100 mg once daily for use with strong CYP3A inhibitors and 200 mg once daily for use with moderate CYP3A inhibitors. After discontinuation of the concomitant strong or moderate CYP3A inhibitors, the entrectinib dose that was taken prior to initiating the strong or moderate CYP3A inhibitor can be resumed. A wash-out period may be required for CYP3A4 inhibitors with a long half-life (see sections 4.2, 4.4 and 4.5 of the SmPC).

Although, a marked effect of inhibitory P-gp drugs on entrectinib pharmacokinetics is not expected, caution is advised when treatment with strong or moderate P-gp inhibitors (e.g. verapamil, nifedipine, felodipine, fluvoxamine, paroxetine) are co-administered with entrectinib due to risk of increased entrectinib exposure. See sections 4.5 and 5.2. of the SmPC.

Co-administration of a proton pump inhibitor (PPI), lansoprazole with a single 600 mg entrectinib dose reduced entrectinib AUC by 25% and C_{max} by 23%.

No dose adjustments are required when entrectinib is co-administered with PPIs or other drugs that raise gastric pH (e.g., H2 receptor antagonists or antacids) (see section 4.5 of the SmPC).

Relationship between exposure response

Because the majority of subjects included in the exposure response analysis received the same dose of entrectinib, it is not possible to conclude that a plateau of efficacy has been reached at the dose of 600 mg QD. The logistic regression models for investigation of the relationship between exposure and adverse event indicate that the probability of an SAE or AE is higher with higher exposure.

With regards to the exposure-QT analysis, a major drawback is that all patients in the study received only one dose, 600 mg QD, of entrectinib, the recommended therapeutic dose. No placebo-control, nor a positive control were included in the QT-assessment. In addition, time-matched baseline ECG recordings were not collected, which would allow for the detection of diurnal patterns in the QTc data. A concentration-QTcF model was developed, where both the concentration of entrectinib and the major metabolite, M5, were investigated in relation to QTcF. A systematic bias is observed in the Predicted versus Observed QTcF plots, which indicates model misspecification. The model predictions are negatively biased at high values which indicates that a PK/PD hysteresis is ignored (i.e. highest delta-QTcF is not observed at Cmax).

Therefore a specific posology recommendation is given in section 4.2 of the SmPC and a warning on QTc prolongation has been added in section 4.4 of the SmPC (see discussion on clinical safety).

2.4.5. Conclusions on clinical pharmacology

Overall, entrectinib PK/PD profile has been characterised in adults. The dose recommendation to treat solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion in adolescents aged 12 years and older is based on data from popPK analysis and is considered acceptable.

2.5. Clinical efficacy

The clinical development programme of entrectinib includes the three ongoing Phase I studies ALKA (adults), STARTRK-1 (adults) and STARTRK-NG (paediatric) and one Phase II study STARTRK-2 (adults). All studies included patients with NTRK1/2/3, ROS1 or ALK molecular alterations. All studies are ongoing.

Within this submission, the Applicant is seeking two separate indications for entrectinib (NTRK fusion positive solid tumors and ROS1 positive advanced NSCLC). For each indication separately, efficacy data from the three adult studies were pooled and analysed collectively.

The paediatric study STARTRK-NG was not included in the integrated efficacy analyses, and have been presented separately to support the activity of entrectinib in paediatric tumours with NTRK fusion. Efficacy data from paediatric patients treated with entrectinib via compassionate access are also provided as supportive information.

Table 19: Summary of entrectinib clinical studies and patients contributing to NTRK and ROS1 NSCLC Efficacy Evaluations

Protocol No.	Study Design	Objective(s) of the Study/Report	Entrectinib Dose, Route and Regimen	Patient Population	Duration of treatment	Study Status
ALKA (ALKA-372-001, GO40783)	First-in-human, Phase I, multicenter, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme	First cycle DLTs and MTD under 3 different schedules. Safety, tolerability, PK, and antitumour activity	Schedule A: 100, 200, 400, 800, 1200, or 1600 mg/m^2/day F1, once daily (fasted) 4-days on, 3-days off schedule × 3 weeks followed by 7-day rest[a] Schedule B: 200 or 400 mg/m2/day or 600 mg/day continuous PO once daily (fed) in a 4-weeks cycle[b] Schedule C: 400 or 800 mg/m2/day once daily in a continuous 4-days on, 3-days off schedule PO (fed)[c]	Adult patients with advanced/ metastatic solid tumours, including patients with TRKA/B/C, ROS1, or ALK molecular alterations	Until progressive disease, withdrawal of patient consent, or unacceptable toxicity	First enrollment: 26/10/2012 Ongoing (accrual completed on 20/3/2018)
STARTRK-1 (GO40784, RXDX-101-01)	Phase I, single-arm, multicenter, open-label, dose escalation and expansion, ascending-dose study with dose escalation according to a standard 3+3 scheme	Dose Escalation: First cycle DLTs, MTD, RP2D, and antitumour activity Dose Expansion: efficacy (ORR) Safety, tolerability, PK, and PD	All cohorts: entrectinib PO once daily (fed) in a continuous daily dosing regimen for 28 consecutive days 100, 200, 400 mg/m^2/day (F1); 800 mg/day (F1); 600 mg/day if BSA≤1.85 m^2 F1 or 800 mg/day if BSA>1.85 m^2 F1; 600 mg/day F1 or F2A	Adult patients with solid tumours harboring NTRK1/2/3, ROS1, or ALK molecular alterations (mandatory for the dose expansion phase)	Until progressive disease, unacceptable toxicity, withdrawal of consent, or loss of clinical benefit	First enrollment: 30/7/2014 Ongoing
STARTRK-2 (GO40782, RXDX-101-01)	Phase II, global, single-arm, open-label, multicenter, basket study	Efficacy (CNS separately), safety, tolerability, PK, population PK, ventricular repolarization, and patient reported outcomes	Entrectinib 600 mg QD F2A (fed), in a continuous daily dosing regimen in 4- week cycles	Adult patients with solid tumours with NTRK1/2/3, ROS1, or ALK gene fusions (excluding ALK positive NSCLC)	Until progressive disease, unacceptable toxicity, withdrawal of consent, or loss of clinical benefit	First enrollment: 16/11/2015 Ongoing
STARTRK-NG (CO40778, RXDX-101-03)	Phase I/Ib, single-arm, multicenter, open-label, 5-part, dose escalation and expansion study	MTD or RP2D in children and adolescents, safety profile, PK, efficacy parameters, intracranial tumour response in CNS patients	Entrectinib PO once daily (fed) with F1, in a continuous daily dosing regimen with 4-week cycles. Dosing as per nomogram ranging from 250–750 mg/m2/day	Children and adolescents (2-22 years) with recurrent or refractory solid tumours and primary CNS tumours, with or without TRK, ROS1, or ALK fusions/ molecular alterations	Until progressive disease, unacceptable toxicity, or discontinuation at the discretion of the subject/ parent/ guardian or Investigator	First pt screened: 2/5/2016 Ongoing

ALK: anaplastic lymphoma kinase; BSA: body surface area; CNS: central nervous system; NSCLC: non-small cell lung cancer; NTRK1/2/3: neurotrophic tyrosine receptor kinase 1/2/3; PO: per os; F1: formulation 1; F2a: formulation 2A; n/a: not applicable

Enrollment status of the adult studies is presented below:

Table 20: **Enrolled Patients up to Enrollment Cut-off of 31 October 2018**

Study	Enrolled patients up to enrollment cut-off of 31 October 2018				
	Total	NTRK gene fusion-positive		ROS1-positive NSCLC	
		Total	Eligible for integrated analyses Data cut-off 31 Oct 2018	Total	Eligible for integrated analyses Data cut-off 31 Oct 2018
ALKA	61	1	1	12	9
STARTRK-1	83	4	2	18	8
STARTRK-2	335	108	90	183	145

2.5.1. Dose response study(ies)

The selection of the entrectinib clinical dosing regimen is based principally on efficacy and safety data from the dose escalation of the phase STARTRK-1 study, concurrently with the first-in-human dose-escalation study ALKA. Real-time data from the dose-escalation evaluations from each study were used to inform both studies. Selection of the entrectinib clinical dosing regimen in adult patients is supported by the clinical safety, efficacy, graphical PK/PD analysis of dose ranging data and exposure response analyses. Cumulatively, the overall data lead to chose for entrectinib a 600 mg once daily dosing.

ALKA

A Phase 1, dose escalation study of entrectinib (RXDX-101) in adult patients with advanced/ metastatic solid tumours (ALKA-372-001)

Methods

Study participants

Consenting adult (age≥18) patients with histologically or cytologically confirmed diagnosis of advanced/metastatic solid tumours with ALK positive alterations (per original protocol) or ALK negative patients with TRKA, TRKB, TRKC, or ROS1 genetic alterations (ALK negative patients with TRKA or ROS1 genetic alterations only up to protocol amendment 5) in patients for whom no alternative effective standard therapy was available, standard therapy was considered unsuitable, or had been refused (per protocol amendment 8), were eligible for the study.

Other main selection criteria included: ECOG PS ≤2; life expectancy of at least 3 months; baseline laboratory data indicating acceptable hematologic status, liver and renal function; resolution of any acute toxic effects (excluding alopecia) of any prior anticancer therapy (NCI CTCAE v 4.03 grade ≤1 or to the baseline laboratory values); tissue available for analysis.

Patients with controlled asymptomatic CNS involvement were eligible in absence of therapy with anticonvulsant (from protocol amendment 8, non-enzyme-inducing anti-epileptic drugs were allowed). Steroids at stable dose (≤4 mg/day dexamethasone or equivalent) for at least 2 weeks were allowed.

Prior cancer therapy was allowed including crizotinib, ceritinib (added with protocol amendment 6) and other investigational drugs. From protocol amendment 8 onwards, prior TRK, ROS1, or ALK (all other than NSCLC patients only) inhibitors were no longer allowed in patients who had tumours harboring those respective molecular alterations.

Treatments

- Schedule A: 4 days on, 3-days off schedule for 3 weeks, followed by a 7-day rest period in a 4-week cycle; fasted condition; once daily.

- Schedule B (added at protocol amendment 3): continuous daily dosing in a 4-week cycle; fed condition; once daily.

- Schedule C (added at protocol amendment 3): 4 days on, 3-days off schedule in a 4-week cycle; fed condition; once daily.

A conventional "3+3" patient enrollment scheme was followed for the dose escalation. Patients could continue study treatment until disease progression, patient refusal, withdrawal of consent, or unacceptable toxicity.

Objectives

Primary Objective: to determine the first cycle DLTs and the MTD.

Secondary Objectives: to define the safety profile, to evaluate the pharmacokinetics in plasma, and to document any antitumour activity of entrectinib.

Endpoints

Primary endpoint: first cycle DLTs and MTD.

Secondary endpoints:

- Overall safety profile of entrectinib

- PK parameters

- Objective tumour response as measured using RECIST v1.1 as determined by investigator (DOR, SD duration, PFS and OS were exploratory analyses).

On treatment tumour assessment was repeated at the end of every even (i.e. end of cycle 2, 4, 6 etc., per the original protocol) or odd cycle (per protocol amendment 6) and at the end of last treatment cycle, if more than 4 weeks had passed from last tumour imaging. For patient treated for longer than 12 cycles, assessment was performed every 3 cycles (per protocol amendment 6). Patients with responding tumours (CR or PR) were required to have the response confirmed at least 4 weeks after the 1st documentation of response. Amendment 8 allowed a blinded independent central review of imaging for retrospective (ongoing patients) and prospective (newly enrolled patients).

Sample size

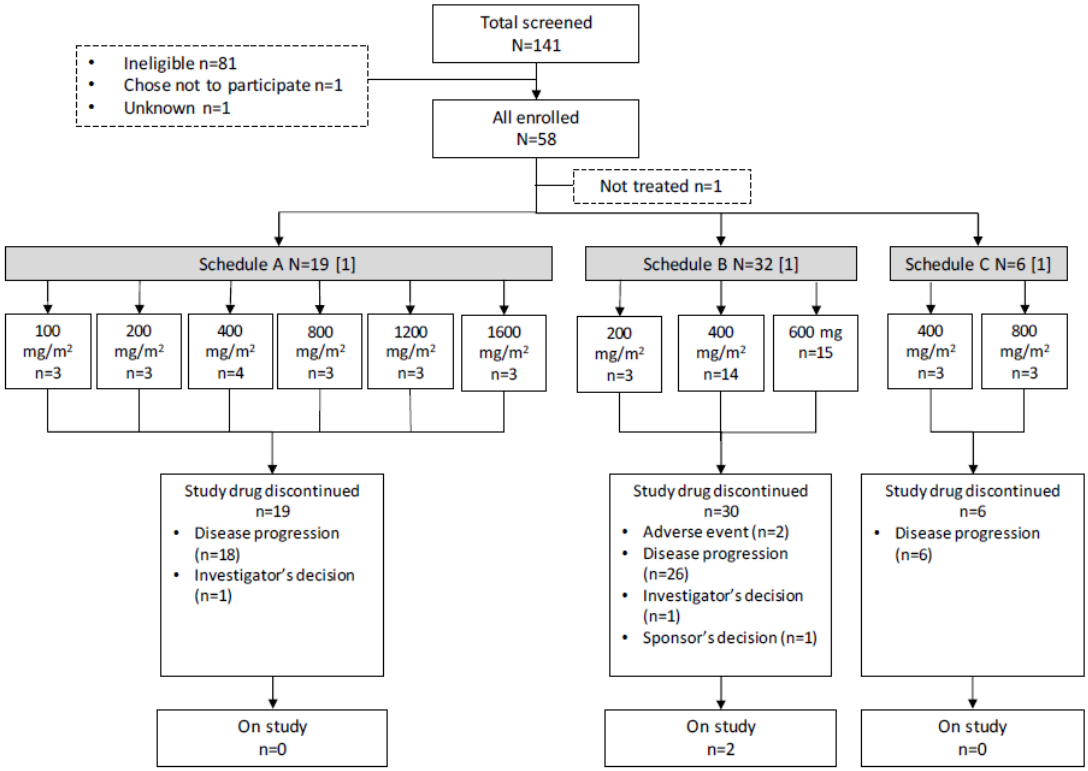
Number of subjects planned to be enrolled was 70. The total number of patients enrolled and treated could vary, depending upon the toxicity observed and the resulting influence on cohort size and number of dose levels tested.

Statistical methods

Efficacy analyses were carried out on treated and evaluable patients. Point estimates with 95% confidence intervals (CIs) are calculated for efficacy endpoints (ORR, DOR, SD duration, PFS, and OS). Time-to-event endpoints were summarized using the Kaplan-Meier method. No formal significance testing was performed. Missing data were not imputed. The possibility of a CSR be written prior to the official end of the study was added by a protocol amendment.

Results

Participant flow



[1] All entrectinib doses were received once daily

Source: Table 14.1.3 and Appendix 16.2.1.1.1
Schedule A: Entrectinib dosing 4-days on, 3-days off for 3 weeks; then 7-day rest period in a 4-week cycle; fasted; once daily.
Schedule B: Entrectinib continuous daily dosing in a 4-week cycle; fed; once daily.
Schedule C: Entrectinib dosing 4-days on, 3-days off in a 4-week cycle; fed; once daily.

Recruitment

Patients were enrolled from 26 Oct 2012 to 20 Mar 2018 in two sites in Italy. Data provided includes patients enrolled up to 30 Nov 2017, with a clinical cut off date (CCOD) of 31 May 2018. As of 30 Nov 2017, 58 patients were enrolled, and 57 received entrectinib. The study is ongoing. Two patients were still receiving treatment at the CCOD.

Conduct of the study

The protocol for this study was approved on 23 Jan 2012. During the study, 10 protocol amendments were implemented. Patient enrollment was initiated with the first amendment dated 05 Mar 2012.

Baseline data

Tumour molecular characterization performed before starting treatment with entrectinib showed the presence of a TRKA/B/C, ROS1, or ALK molecular alterations in all treated patients except for patient ##0055 who had SCLC without genetic alterations of interest but enrolled in the study with a waiver. Patient ##0004 was enrolled in the study based on the molecular analysis performed at the local laboratory (which is not reported; molecular analysis was later confirmed by central molecular diagnosis).

Numbers analysed

Overall, 58 patients with advanced/ metastatic solid tumours with TRKA/B/C, ROS1, or ALK positive genetic alterations were enrolled, 57 received entrectinib, 54 patients were evaluable for DLT and 54 for efficacy.

Outcomes and estimation

DLTs and MTD: No DLTs were reported in this study and, consequently, no MTD could be defined for any of 3 schedules investigated. Because drug exposure was in the predicted efficacious range and preliminary antitumour activity was observed, 400 mg/m2 was declared the BSA-based RP2D of entrectinib.

STARTRK-1

This study included a dose escalation and a dose expansion segment. As no patients were enrolled in the ongoing dose expansion as of the enrollment cut off of 30 Nov 2017, data from the dose expansion segment has not been included in the submission.

A Phase 1, Multicenter, Open-Label Study of Oral Entrectinib (RXDX-101) in Adult Patients With Locally Advanced or Metastatic Cancer Confirmed to be Positive for NTRK1, NTRK2, NTRK3, ROS1, or ALK Molecular Alterations (RXDX-101-01).

Methods

Study participants

Adult patients (age ≥18) with a histologically or cytologically confirmed diagnosis of relapsed or refractory locally advanced or metastatic solid tumours for whom no alternative effective standard therapy was available or for whom standard therapy was considered unsuitable or intolerable were enrolled. A molecular alteration in NTRK1, NTRK2, NTRK3, ROS1, or ALK was preferred, but not a requirement for patient eligibility in the dose escalation, while it was required in the dose expansion segment.

Other main inclusion criteria included: measurable or evaluable disease assessed locally using RECIST v1.1; ECOG PS ≤2; life expectancy of at least 3 months; acceptable baseline laboratory values as per protocol; resolution of all acute toxic effects (excluding alopecia) of any prior anticancer therapy to NCI CTCAE (v4.03) grade ≤1 or to the baseline laboratory values.

Patients with controlled asymptomatic CNS involvement were allowed in the study. Seizure prophylaxis was allowed if with non-enzyme-inducing anti-epileptic drugs (non-EIAEDs). Patients requiring steroids must have been at a stable or decreasing dose (≤8 mg/day dexamethasone or equivalent) for at least 2 weeks prior to entrectinib treatment start.

Prior cancer therapy was allowed, including crizotinib, ceritinib, and investigational drugs. Prior radiotherapy was allowed if >14 days had elapsed since end-of-treatment visit.

Tumour tissue available for analysis was not required in the dose escalation segment but was desired (if clinically feasible) for the dose expansion segment.

Treatments

Dose escalation segment: all patients in each dose cohort received entrectinib orally for 28 consecutive days (for patients enrolled between protocol v2 [26 Mar 2014] and protocol v4 [08 Oct 2014], cycle 1 was 42 consecutive days and all subsequent cycles were 28 days). The starting dose was 100 mg/m^2 (based on BSA), once daily, administered within 60 minutes following a meal. A conventional "3+3" patient enrollment scheme was followed.

Dose expansion segment: all patients received entrectinib at the RP2D determined during the dose escalation segment (600 mg OD in repeated 4 weeks cycles)

Treatment with entrectinib continued until progressive disease, withdrew consent, or unacceptable toxicity. In cases of progressive disease, after discussion with the sponsor, treatment could continue if the investigator believed that the patient might continue to derive clinical benefit.

Two entrectinib formulations (F1 and F2A) were used in this study.

Objectives (dose escalation segment)

Primary objective:

- to determine the first cycle DLTs, the MTD, and a biologically effective and RP2D.

Secondary objectives:

- Safety profile
- PK of entrectinib (and its potential metabolites) in plasma
- Antitumor activity
- Assay methods to detect molecular alterations (as defined in biomarker assessments), and identify appropriate analytical cutoffs and other relevant biomarker parameters that predict antitumour activity of entrectinib

Pharmacodynamics (PD) of entrectinib on molecular targets in tumour and surrogate tissue

Endpoints (dose escalation segment)

Primary endpoint:

- first cycle DLTs, MTD, and the RP2D

Secondary endpoints:

- Safety
- PK parameters
- Efficacy parameters (ORR by RECIST 1.1, PFS, OS, CBR, DOR)
- PD profile
- Tumour assessment: Tumour imaging was performed at the end of cycle 1, then every 8 weeks thereafter (ie, end of cycles 3, 5, 7, etc, or whenever a clinical deterioration was observed) and at the end-of-treatment visit. For patients with CR or PR, response confirmation was required to be performed no less than 4 weeks from when response criteria were first met.

Sample size

The dose escalation segment of the study is designed as a Phase 1 study with safety and treatment tolerability as its primary objectives. No power calculations were done. Updated sample size included at least 15 patients.

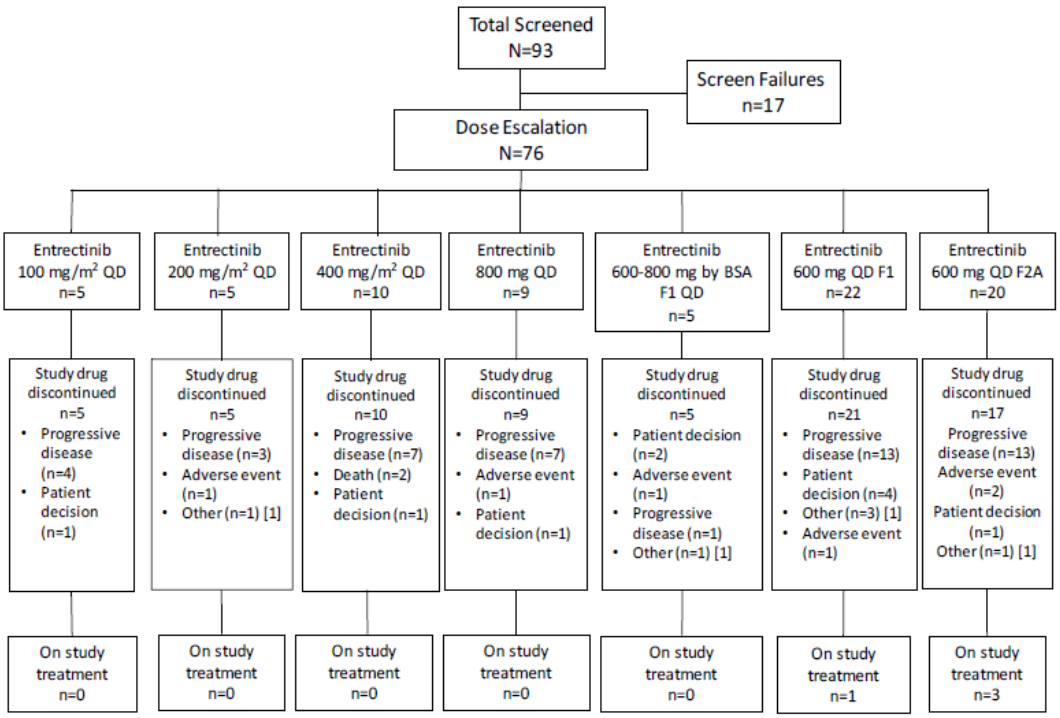
Statistical methods

Summary statistics were used to present data, with 95% confidence intervals (CIs). Time-to-event endpoints (PFS, OS, and DOR) were calculated from start date to the date of the applicable event and were reported in months. PFS and OS were to be analyzed in all treated patients (ie, the safety analysis set), however, these analyses were performed using the efficacy analysis set to align all

efficacy endpoints for the same population. Time-to-event endpoints were summarized using the Kaplan Meier estimates. No formal significance testing was performed. Missing data were not imputed except for partially missing dates.

Results

Participant flow



Source: Table 14.1.3 and the Interactive Web Response System spreadsheet (provided in the Trial Master File)
Two entrectinib release formulations (F1 and F2A) were used in this study.
[1] "Other" reasons for study treatment discontinuation included the following: clinical progression and clinical judgement (Appendix 16.2.1.1)
BSA, body surface area; QD, once daily.

Recruitment

Patients were recruited in 11 centers in the United States (n=8), Spain (n=2), and South Korea (n=1). First enrolment occurred on 30 July 2014. The study is ongoing.

Conduct of the study

The original protocol, dated 25 February 2014, was amended 6 times during the study. Additionally, the modified Fibonacci scheme that was planned for the dose escalation segment was not followed as information from the ALKA study was used to direct dose escalation after the 400 mg/m2 dose.

Baseline data (dose escalation)

Table 21: Disease Characteristics (molecular alteration) – Dose Escalation (Safety Analysis Set)

Characteristic/History	Dose of Entrectinib QD							
	100 mg/m² F1 (N=5)	200 mg/m² F1 (N=5)	400 mg/m² F1 (N=10)	800 mg F1 (N=9)	600-800 mg by BSA F1	600 mg F1 (N=22)	600 mg F2A (N=20)	Overall (N=76)
Molecular Characterization of Tumour, n (%)								
TRKA	2 (40.0)	0 (0.0)	1 (10.0)	2 (22.2)	1 (20.0)	4 (18.2)	1 (5.0)	11 (14.5)
TRKB	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (4.5)	1 (5.0)	3 (3.9)
TRKC	0 (0.0)	3 (60.0)	2 (20.0)	1 (11.1)	0 (0.0)	1 (4.5)	2 (10.0)	9 (11.8)

ROS1	0 (0.0)	1 (20.0)	1 (10.0)	1 (11.1)	2 (40.0)	8 (36.4)	11 (55.0)	24 (31.6)
ALK	3 (60.0)	1 (20.0)	5 (50.0)	3 (33.3)	1 (20.0)	6 (27.3)	5 (25.0)	24 (31.6)
NA	0 (0.0)	0 (0.0)	1 (10.0)	1 (11.1)	1 (20.0)	2 (9.1)	0 (0.0)	5 (6.6)

Numbers analysed

The DLT analysis set (dose escalation) included 14 patients. The safety analysis set included 76 patients and the efficacy analysis set included 68 patients.

Outcomes and estimation

Primary endpoints

DLT: Three patients in the 800 mg dose group had 1 DLT each: grade 3 fatigue (002-108), grade 3 disturbance in attention (003-105), grade 3 fatigue (005-105; this occurred after the decision was made to lower the dose to 600 mg based on the previous two DLTs).

RP2D: During dose escalation, because no DLTs were reported, 400 mg/m2 was declared the BSA-based RP2D of entrectinib. At the 400 mg/m2, drug exposure was predicted efficaceous range, and preliminary antitumor activity observed. Per the protocol, at the BSA-based RP2D, administration of a flat dose was to be considered; therefore, patients were enrolled at a once daily dose of 800 mg. As DLT were observed at the 800 mg flat dose, 600 mg once daily on a continuous daily dosing regimen was declared as the RP2D of entrectinib (decision based also on favourable tolerability, exposure and preliminary antitumor activity of 600 compared to 800).

Secondary endpoints

ORR by RECIST 1.1 (confirmed CR or PR)

Table 22: Objective Response Rate – Dose Escalation (Efficacy Analysis Set)

	Dose of Entrectinib QD							
	100 mg/m² F1 (N=5)	**200 mg/m² F1 (N=5)**	**400 mg/m² F1 (N=10)**	**800 mg F1 (N=9)**	**600-800 mg by BSA F1 (N=4)**	**600 mg F1 (N=20)**	**600 mg F2A (N=15)**	**Overall (N=68)**
Best Overall Response, n (%)								
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.5)
PR	0 (0.0)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	5 (25.0)	5 (33.3)	12 (17.6)
Stable disease	0 (0.0)	1 (20.0)	2 (20.0)	1 (11.1)	1 (25.0)	6 (30.0)	4 (26.7)	15 (22.1)
PD	3 (60.0)	3 (60.0)	4 (40.0)	6 (66.7)	0 (0.0)	6 (30.0)	4 (26.7)	26 (38.2)
	2 (40.0)	1 (20.0)	2 (20.0)	2 (22.2)	3 (75.0)	2 (10.0)	2 (13.3)	14 (20.6)
Objective Response Rate (confirmed CR+PR), n	0 (0.0)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	6 (30.0)	5 (33.3) (11.8, 61.6)	13 (19.1) (10.6,
Clinical Benefit Rate (CR+PR+stable disease >6 months), n (%) 95% Confidence Interval [1] [2]	0 (0.0)	0 (0.0)	3 (30.0)	1 (11.1)	0 (0.0)	7 (35.0)	5 (33.3) (11.8, 61.6)	16 (23.5) (14.1, 35.4)

Two entrectinib formulations (F1 and F2A) were used in this study. Percentages of patients were calculated based on the number of patients in each dose group in the efficacy analysis set. Please refer to SAP for the calculation of these rates. RECIST v1.1. criteria were employed.

[1] Confidence intervals were given for the 600 mg F2A group and the Overall population.

[2] Patients were included if they have stable disease for at least 168 days.

BSA, body surface area; CR, complete response; PR, partial response; PD, progressive disease; QD, once daily; NE, not evaluable; RECIST, Response Evaluation Criteria in Solid Tumors; SAP, statistical analysis plan.

2.5.2. Main study(ies)

An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor NTRK1/2/3, ROS1, OR ALK Gene Rearrangements (GO40782, STARTRK-2).

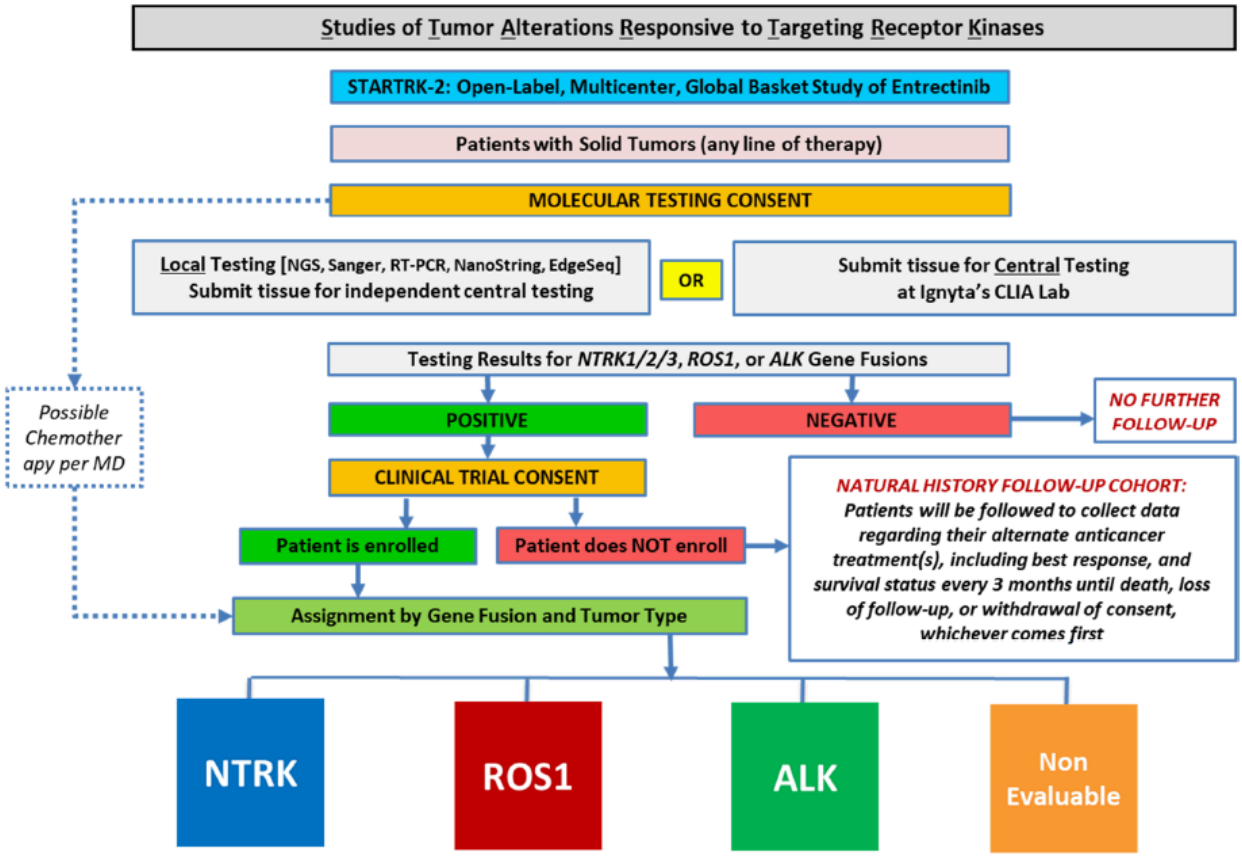


Figure 9: STARTRK2 Basket Study Schema

A "natural history follow-up cohort" included only 12 patients up to Nov 2017.

Methods

Study Participants

- Adult patients (≥18 years) who signed consent form with histologically- or cytologically-confirmed locally advanced or metastatic solid tumor that harbors an NTRK1/2/3, ROS1, or ALK gene rearrangement that is predicted to translate into a fusion protein with a functional TRKA/B/C, ROS1, or ALK kinase domain, respectively, without a concomitant second oncodriver (e.g. epidermal growth factor receptor, KRAS) as determined by Ignyta's CAP/CLIA laboratory or by any nucleic acid-based diagnostic testing method performed at a local CLIA-certified or equivalently-accredited diagnostic laboratory.
- Measurable disease as assessed locally using the RECIST v1.1 (patients with non-measurable disease were eligible for enrollment in the "non-evaluable" basket).
- Patients with CNS involvement, including leptomeningeal carcinomatosis, which is either asymptomatic or previously-treated and controlled, are allowed. Seizure prophylaxis is allowed

with non-EIAEDs only. Patients requiring steroids must be at stable or decreasing doses for at least 2 weeks prior to the start of entrectinib treatment.

- Prior anticancer therapy is allowed (excluding approved or investigational TRK, ROS1, or ALK (non-NSCLC patients only) inhibitors in patients who have tumors that harbor those respective gene rearrangements). Prior radiotherapy is allowed if more than 14 days have elapsed since the end of treatment. Patients who received brain irradiation must have completed whole brain radiotherapy at least 14 days prior and/or stereotactic radiosurgery at least 7 days prior to the start of entrectinib treatment.
- ECOG performance status ≤2 and minimum life expectancy of at least 4 weeks
- Adequate liver function (AST and ALT≤3.0×ULN; ≤5.0×ULN if liver metastases are present; total serum bilirubin ≤2.0×ULN; patients with a known history of Gilbert's syndrome and/or isolated elevations of indirect bilirubin are eligible).
- Females of childbearing potential must have a negative serum pregnancy test during Screening and must not be breastfeeding or intending to become pregnant during the study.
- Ability to swallow entrectinib intact without chewing, crushing, or opening the capsules.

Key Exclusion Criteria:

- History of other previous cancer that would interfere with the determination of safety or efficacy of entrectinib with respect to the qualifying solid tumor malignancy.
- Incomplete recovery from any surgery.
- Any condition (in the past 3 months) that would interfere with the determination of safety or efficacy of entrectinib: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, stroke, symptomatic bradycardia, or uncontrolled arrhythmias requiring medication.
- History of non-pharmacologically induced prolonged QTc interval (e.g., repeated demonstration of a QTc interval ≥500 milliseconds from ECGs performed at least 24 hours apart).
- History of additional risk factors for torsade de pointes (e.g., family history of long QT syndrome).
- Peripheral neuropathy Grade ≥2.
- Known active infections (bacterial, fungal, or viral, including HIV positive).
- Active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would reasonably impact drug absorption.
- Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis. Note: Radiation-induced lung disorders are not included in this exclusion criterion.

Treatments

Entrectinib 600 mg orally once-daily on a continuous daily dosing regimen in 4-week cycles.

Patients were treated until documented radiographic progression as assessed by BICR, development of unacceptable toxicity, or withdrawal of consent. Patients could continue treatment with entrectinib

after BICR-confirmed disease progression if the patient was perceived to be deriving clinical benefit. For these patients, tumor assessments were no longer submitted for BICR.

Objectives

Primary objective:

- To determine the ORR of entrectinib, as assessed by blinded independent central review (BICR), in each patient population basket of solid tumors that harbor an NTRK1/2/3, ROS1, or ALK gene rearrangement.

Secondary objectives:

- To determine DOR, TTR, and CBR of entrectinib, as assessed by BICR, in each patient population basket of solid tumors that harbor an NTRK1/2/3, ROS1, or ALK gene rearrangement
- To determine the intracranial tumor response of entrectinib and CNS progression-free survival (CNS-PFS) in patients presenting with measurable CNS disease at baseline, as assessed by BICR using RANO or RANO-BM, as applicable
- To estimate the PFS and OS of patients with solid tumors that harbor an NTRK1/2/3, ROS1, or ALK gene rearrangement treated with entrectinib
- To evaluate the safety and tolerability of entrectinib when administered at the RP2D in patients with solid tumors that harbor an NTRK1/2/3, ROS1, or ALK gene rearrangement
- To assess the population pharmacokinetics (PK) of entrectinib and to explore correlations between PK, response, and/or safety findings in patients with NTRK1/2/3, ROS1, or ALK gene rearrangements
- To evaluate the effect of entrectinib on ventricular repolarization
- To assess treatment-related symptoms and general health status using validated instruments of patient reported outcomes

Exploratory objectives (to be reported separately):

- To assess any potential differences in clinicopathologic presentation and response to entrectinib among the various tumor types harboring NTRK1/2/3, ROS1, or ALK gene rearrangements
- To gain insights into potential mechanisms of resistance to entrectinib

Outcomes/endpoints

Primary endpoint:

- ORR (confirmed response = persisted on repeated-imaging≥4 weeks after initial documentation of response)

Secondary endpoints:

- DOR, TTR, CBR (CR, PR, or SD at 6 months after the first dose of entrectinib), Intracranial tumor response in patients with measurable CNS disease, as determined by BICR using RANO or RANO-BM, as applicable, CNS progression free survival (CNS-PFS) in patients with measurable CNS disease, PFS, OS

- AEs
- Population PK
- Ventricular repolarization
- Quality-of-life and health status

Exploratory endpoints:

- Analysis of potential differences in clinicopathologic presentation and response to entrectinib among the various tumor types harboring NTRK1/2/3, ROS1, or ALK gene rearrangements
- Potential mechanisms of resistance to entrectinib
- All radiographic efficacy endpoints were based on BICR using RECIST v1.1 (except for patients with CNS disease where radiographic confirmation of intracranial objective tumor response or disease progression was based on RANO or RANO-BM).
- Tumor assessments were performed at Screening, at the end of Cycle 1 and every 8 weeks, and at the End of Treatment (if more than 4 weeks had passed since the last imaging assessment). Radiographic confirmation of objective tumor response (no earlier than 4 weeks from the first response) or disease progression was based on RECIST v1.1 and assessed both locally and by BICR. Stable disease can be assigned only after a patient meets stable disease criteria for at least 5 weeks (≥35 days) following the first dose of treatment. At Screening, a CT/MRI of the brain was obtained to rule out newly diagnosed, untreated brain metastases or to document stability of previously treated brain metastases. If brain metastases were not documented at Screening, then brain scans were performed as clinically indicated.

Sample size

For each basket evaluable for the primary endpoint, a 2-stage sequential testing design was adopted, with up to 62 patients needed to be enrolled. By assuming at least 80% power and 1-sided alpha=0.025, and by considering a true response rate of 20% or less insufficient to warrant further study, whereas a true response rate of 40% or more worthy of further study, the number of patients evaluated in each stage and the minimum number of responders needed to meet the primary endpoint were determined. In the first stage up to 13 patients are enrolled sequentially per basket. The stage was deemed successful on the 4th responder and the second stage was considered. In the second stage additional 49 patients need to be enrolled sequentially per basket, and the stage was deemed as having met the primary endpoint if the 14th responder was observed prior to the enrollment of the 49th response-evaluable patient in stage 2.

Moreover, for the ROS1-Positive, ROS1 Inhibitor-Naïve NSCLC Basket, based on expected response rate to crizotinib, after completion of the two stage design (Part A), a further study (Part B) was planned to rule out a statistically significant BICR-ORR<=50%, by assuming the true ORR is at least 65%, power of 80% and 1-sided alpha=0.025. In this phase, 90 additional treated patients were needed. A pooled analysis of safety and efficacy of Parts A and B was planned, with approximately 150 (=62+90) ROS1-positive, ROS1 inhibitor-naïve NSCLC patients treated with entrectinib at the RP2D. Such sample size, allows to rule out an ORR <=50% when the true ORR is at least 65% at a 1-sided alpha=0.025 and >90% power.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

Each study basket was considered an independent study. All efficacy analyses were performed for the Efficacy Evaluable Analysis Population (EE) populations of NTRK fusion-positive solid tumors and ROS1-positive NSCLC, unless otherwise specified.

ORR was reported as the proportion of responders along with the corresponding 2-sided 95% Clopper-Pearson exact confidence interval (CI). Clinical Benefit Rate (CBR) was reported as the proportion of patients achieving the clinical benefit with corresponding 2-sided 95% Clopper-Pearson exact CI. Intracranial Tumor Response (IC-ORR): were reported as the proportion of patients achieving intracranial tumor response on the total number of patients with brain metastases at baseline, with corresponding 2-sided 95% Clopper-Pearson exact confidence interval. Time to Event data (DOR, TTR, PFS, time to CNS progression, IC-PFS, and OS) were summarized by median, 25th, and 75th percentiles estimated using the Kaplan-Meier method. The associated 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) and Klein and Moeschberger (1997). Landmark analyses (e.g., duration rates at 6 months, 9 months, 12 months, and 18 months) were provided with their corresponding 95% CIs calculated using the method of Kalbfleisch and Prentice (1980). Median follow-up was estimated using the reverse Kaplan-Meier method (Schemper and Smith. 1996). Depending on available sample size (n >=5), subgroup analyses of safety and efficacy were performed by Age, Sex, Race, Region, ECOG, Number of Lines of Prior Anticancer Therapies, Prior Treatment, Types of prior treatment, Prior radiation, Extracranial vs. intracranial solid tumors. Exploratory analyses to assess concordance between BICR and Investigators assessments of response, and sensitivity analyses of ORR-BICR for the full EA were carried out. Inferential statistics were not generated.

Recruitment

The study was conducted at 84 investigative sites in 15 countries globally. Enrollment started on 16 November 2016 and is ongoing.

The initial protocol was dated 30 July 2015. The latest protocol version number 6 is dated 28 May 2019.

2.5.3. ROS1 positive NSCLC

An integrated efficacy analysis has been presented to support the use of entrectinib for the treatment of patients with ROS1-positive, advanced or metastatic NSCLC. This was conducted based on the ROS1 NSCLC Efficacy Evaluable Analysis Set, composed of adult patients with ROS1-positive NSCLC treated with at least one dose of entrectinib across the three studies in adult patients with solid tumors (ALKA, STARTRK-1, and STARTRK-2). All patients included in the ROS1 NSCLC Efficacy Evaluable Analysis Set had measurable disease at baseline and at least 12 months follow-up from the time of first response.

The ROS1 NSCLC Efficacy Evaluable Analysis set includes n=53 patients enrolled up to 30 April 2017. Of the n=53 patients, 9 were in ALKA, 7 in STARTRK-1 and 37 in STARTRK-2.

A larger dataset of n=94 subjects enrolled up to 30 Nov 2017 was provided per CHMP request (not pre-specified in the iSAP and considered exploratory). In addition to the n=53 patients above, this

dataset include further 41 patients enrolled between 30 April 2017 and 30 Nov 2017, all treated within the STARTRK-2 study.

Methods

Study participants

The enrolled population is defined as the population of patients who were enrolled into 1 or more of the entrectinib studies. For the efficacy analysis, data were pooled across the 3 adult (age ≥18 years) clinical studies ALKA, STARTRK-1 and STARTRK-2. Patients must meet all of the following criteria:

- Have tumors that harbour a ROS1 gene fusion (as defined below)
- Received at least 1 dose of entrectinib
- Has NSCLC
- Not treated previously with a ROS1 inhibitor (eg, crizotinib)

Molecular characterization of tumour tissue:

Assay methods: the molecular characterization of tumour tissue for patients included in the pooled analysis was determined by several methods, including the following:

ALKA: Local FISH or IHC. If tissue is available, independent central testing is performed post enrolment at the following laboratories:

Central laboratory (Niguarda) using FISH and IHC methods

Ignyta CLIA laboratory, using the Trailblaze Pharos NGS testing method

STARTRK-1: Local FISH, real-time polymerase chain reaction (qPCR), IHC, or NGS

STARTRK-2: Local nucleic acid-based methodology from a clinical laboratory improvements amendment (CLIA)-certified or equivalently-accredited diagnostic laboratory, or central testing by Ignyta Trailblaze Pharos NGS testing. For patients enrolled based on the positive interpretation of the local test, tissue, if available, is sent for independent central testing at Ignyta using Trailblaze Pharos.

Patients samples determined to be positive by local testing were re-tested centrally by the Sponsor where possible (method TrailBlaze Pharos).

In STARTRK-2 protocol version 6 (28 May 2019), testing for enrollment eligibility was performed in on of the two ways:

- A representative tumour tissue specimen may be submitted to the central laboratory of Foundation Medicine, Inc. in Cambridge, Massachusetts, USA, or to the alternative, approved central laboratory for that region, to be tested for the presence or absence of target gene rearrangements (fusions) via next generation sequencing (NGS).

- Alternatively, patient specimens may be tested locally using any nucleic acid-based diagnostic testing method that relies on direct assessment of gene rearrangements and is performed in a CLIA-certified or equivalently-accredited diagnostic laboratory. FISH is not an acceptable method. All patients enrolled via local testing will still be required to provide tissue samples as described above to Foundation Medicine, Inc., or to the alternative, approved central laboratory for that region for independent central molecular NGS testing post-enrollment.

Gene fusion status: Only patients harboring gene fusions in NTRK, ROS1, or ALK that are predicted to translate into a fusion protein with a functional kinase domain are considered to have a positive gene-fusion status. Patients having other types of molecular alterations (eg, noncoding gene rearrangements, single nucleotide polymorphisms, over-expression, deletions, amplifications, etc.) are not considered to be positive for a gene fusion. Patients having the NTRK, ROS1, or ALK gene fusion and evidence of co-occurrence with 1 or more other oncogenic drivers (eg, NTRK1 with KRAS or EGFR) are not be considered positive for gene fusion because these patients lack a sole known oncodriver.

Treatments

At least one dose of entrectinib at or above the RP2D of 600 mg.

Objectives

Primary Efficacy Objectives:

- Determine the Objective Response Rate (ORR) of entrectinib as assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Determine the duration of response (DOR) as assessed by BICR using RECIST v1.1

Secondary Efficacy Objectives:

- Determine the clinical benefit rate (CBR) of entrectinib as assessed by BICR using RECIST v1.1
- Estimate the progression-free survival (PFS) as assessed by BICR and overall survival (OS)
- Estimate the time to CNS progression as assessed by BICR using RECIST 1.1

In a subset of patients with CNS disease at baseline by INV, the following were assessed:

- Overall (systemic) ORR as assessed by BICR using RECIST v1.1

- Intracranial ORR (IC-ORR) as assessed by BICR using RECIST v1.1 in patients presenting with measurable CNS lesions at baseline, as well as patients with measurable and nonmeasurable CNS lesions at baseline

- Intracranial DOR (IC-DOR) as assessed by BICR

- Intracranial PFS (IC-PFS) as assessed by BICR

Safety Objectives:

Evaluate the safety and tolerability of entrectinib

Patient Reported Outcomes Objectives (STARTRK-2 only)*:*

Assess treatment-related symptoms and general health status following treatment with entrectinib using validated instruments of patient reported outcomes

Outcomes/endpoints

Primary Endpoints:	
Objective Response Rate (ORR)	Proportion of patients with confirmed CR or PR (responders) per RECIST 1.1 by BICR; a confirmed response was a response that persisted on repeat-imaging ≥4 weeks after initial documentation of response.

	Non-responders included the following: • Patients without a confirmed objective response • Patients without a baseline or post-baseline tumor assessment • Patients who received at least 1 dose of entrectinib and who discontinued for any reason prior to undergoing one post-baseline response evaluation.
Duration of Response (DOR)	Time from the date of first objective response (either CR or PR) to first documentation of radiographic disease progression or the date of death due to any cause, whichever was earlier. Evaluation was based on RECIST 1.1 by BICR. DOR (months) was calculated only for responders. For patients without disease progression or death, DOR was censored at the last tumor assessment date prior to the CCOD.
Best Overall Response (BOR)	Best radiologic overall response recorded at any single time point from the start of treatment until disease progression, based on RECIST v1.1. by BICR. CR or PR required confirmation no earlier than 4 weeks from the first response. SD could have been assigned only after a patient met SD criteria for at least 5 weeks (≥35 days) following the first dose of treatment. Otherwise, the best response was not evaluable. BOR not evaluable included also: no post-baseline scans available and missing subsets of scans at all timepoints. Patients with only non-target lesions could only have been assessed as CR, non-CR/non-PD, PD or not evaluable, as per RECIST v1.1 guidelines.
Secondary Endpoints:	
Clinical Benefit Rate (CBR)	CBR was the proportion of patients who met one of the following criteria (assessed by BICR per RECIST v1.1): • Confirmed CR or confirmed PR SD for at least 6 months following start of entrectinib
Time to CNS Progression	Time (months) from first dose of entrectinib to first documentation of radiographic CNS disease progression or death due to any cause. Radiographic CNS disease progression was defined as an occurrence of a new CNS lesion or progression in any CNS lesion per RECIST v1.1 by BICR. Patients without radiographic CNS progression or death were censored on the date of the last tumor assessment prior to the CCOD. (Note: patients without CNS lesions present at baseline per investigator assessment were not required to have scheduled brain scans every 8 weeks).
Progression-Free Survival (PFS)	Time (months) from first dose of entrectinib to first documentation of radiographic disease progression per RECIST v1.1 by BICR or death due to any cause. Patients without progression or death were censored on the date of the last tumor assessment (or, if no tumor assessment was performed after the baseline visit, at the date of first dose of entrectinib) prior to the CCOD.
Overall Survival (OS)	Time (months) from the first dose of entrectinib to the date of death due to any cause. Patients who were alive at the time of the analysis were censored on the last known date that they were alive on or prior to CCOD. Patients with no post-baseline information were censored on the date of first dose of entrectinib. Patients who were lost to follow-up or withdrew consent for further follow-up were censored on the last known date that they were alive on or prior to CCOD.
Intracranial-specific endpoints (evaluated in the subpopulation presented with CNS disease at baseline)	

Intracranial Objective Response Rate (IC-ORR)	Proportion of patients with confirmed CR or PR in the CNS lesion(s) per RECIST 1.1 by BICR (intracranial responders). Confirmed response persisted on repeat-imaging ≥4 weeks after initial documentation of response. The analysis was performed for patients presenting with measurable CNS lesions at baseline, as well as for patients with only non-measurable CNS lesions at baseline, selecting only CNS lesion(s) (target, non-target, or both, as determined by BICR) for each patient, and applying RECIST v1.1 criteria.
Intracranial-Duration of Response (IC-DOR)	Time from the date of first intracranial response to first documentation of radiographic CNS disease progression (per RECIST 1.1 by BICR) or date of death due to any cause, whichever was earlier. IC-DOR was calculated only for intracranial responders. For patients without CNS disease progression and who did not die within 30 days of the last dose of study treatment, IC-DOR was censored at the last tumor assessment date prior to any date of subsequent anticancer therapy, including surgery or radiotherapy to the brain.
Intracranial Progression-Free Survival (IC-PFS)	Time (months) from first dose of entrectinib to first documentation of radiographic CNS disease progression or death due to any cause. Radiographic CNS disease progression was defined as an occurrence of a new CNS lesion or progression in any CNS lesion per RECIST v1.1 by BICR. Patients without radiographic CNS progression or death were censored on the date of the last tumor assessment prior to the CCOD.

The censoring rules for IC-DOR and DOR were the same, no 30 days criteria was applied, and that all censored patients (at the time of last tumour assessment) were not progressing (intracranially if IC-DOR) /not died at the CCOD.

Tumour assessment:

- Tumour scans for patients in the STARTRK-2 study were evaluated prospectively.

- Tumour scans for patients included in the efficacy-evaluable patient populations from the ALKA and STARTRK-1 studies were evaluated by the same BICR team.

Screening tumour assessments (CT/MRI) of the thorax and abdomen, plus brain were performed 4 weeks prior to the first administration of entrectinib.

Sample size

By assuming the true objective response rate by BICR was 70%, a sample size of at least 50 patients would have yielded a 95% 2-sided confidence interval with precision ±17% that would have excluded a lower limit of 50%.

Statistical methods

Efficacy analyses were carried out on the ROS1 NSCLC efficacy-evaluable population. Summary statistics with 95% 2-sided CIs properly calculated were used.

ORR, CBR, IC-ORR: proportion and corresponding 2-sided 95% Clopper-Pearson exact CI.

Time-to-event endpoints (DOR, PFS, OS, IC-DOR, IC-PFS, Time to CNS progression): median, 25th, and 75th percentiles estimated by using the Kaplan-Meier method. The associated 2-sided 95%CIs were calculated using the method of Brookmeyer and Crowly (1982) and Klein and Moeschberger (1997). Landmark analyses at 6, 9, and 12 months were provided with the corresponding 2-sided 95%

CIs calculated using the method of Kalbfleisch and Prentice (1980). Kaplan-Meier curves will be presented.

Waterfall and swimmer plots were used to depict each patient's best tumor response (BOR) and time on study, respectively, including time to first objective response by BICR (if applicable) and DOR.

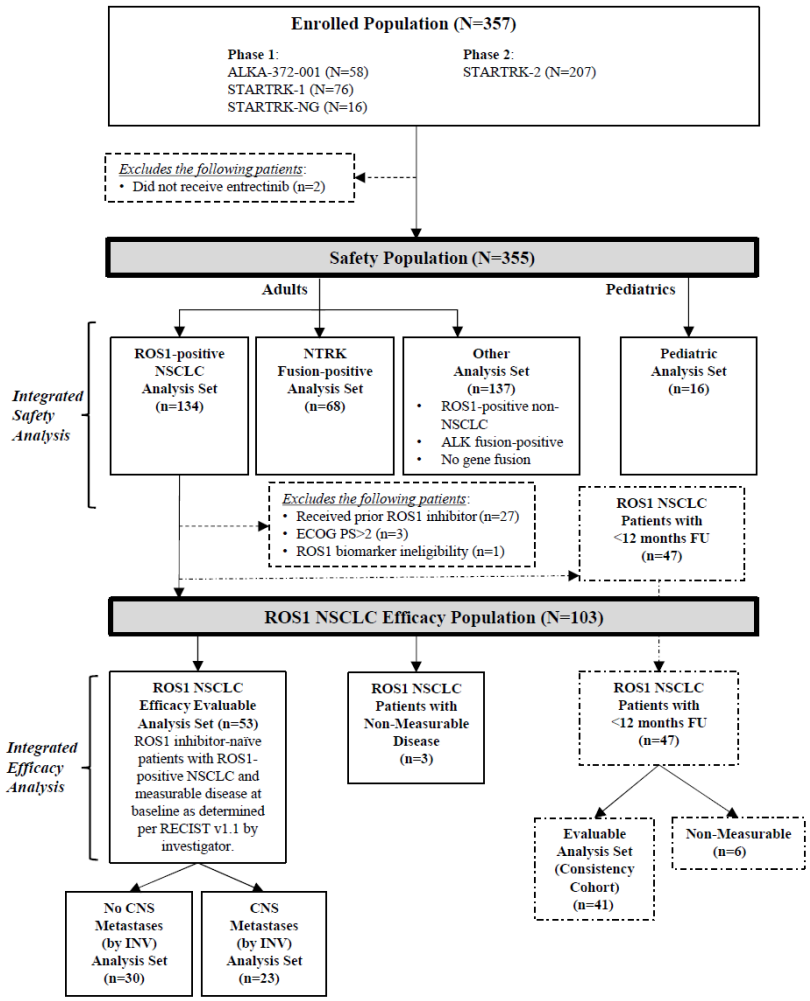
Formal significance tests were not performed. No statistical adjustment was made to address the sources of multiplicity associated with the integrated analysis, nor to account for subgroup effects associated with pooling of data. Statistical analyses were carried out overall, by study, by CNS-disease status at baseline by INV. Sensitivity analyses were carried out to assess robustness of findings. Exploratory analysis on ROS1 NSCLC efficacy nonevaluable population was planned.

Table 23: SAP revision

Revision Date (dd month, yyyy)	**Summary of Revision**	**Reason for Revision**
17 Feb 2017	Initial release	
21 Apr 2017	1. Change NDA submission to marketing application submission; clarify final analysis 95% CI threshold independent of N 2. Added sensitivity analyses of efficacy endpoints by specific *NTRK* fusions: *NTRK1*, *NTRK2*, and *NTRK3* separately. 3. Add analysis of adverse events relative to entrectinib exposure (≤2 cycles vs. ≥3 cycles) 4. Replaced appendix 2 with simplified censoring scenarios for US and ex-US	1. Generalized terminology for submission; clarification of final analysis population sample size criteria. 2. Supportive data to compare to efficacy in pooled *NTRK1/2/3* patient population 3. Evaluate safety profile adjusted for exposure duration 4. Initial release included specific scenarios for US guidance only. Both US and ex-US rules will be implemented for PFS analyses.
02 Aug 2017	1. Clarify objectives for patients with CNS disease at baseline; move RANO-BM to exploratory 2. Add Individual Compassionate Use (ICU) protocol patients 3. Modify the phase 2 eligible population to include patients treated with at least 1 dose of entrectinib 4. Clarify gene fusion population excludes those with dual oncogenic driver 5. Clarify handling of patients enrolled prior to Amendment 3 who meet criteria for Non-evaluable analysis set	1. Patients with CNS disease at baseline include those with measurable and those with measurable and nonmeasurable; RANO-BM is exploratory: IC-ORR is preferred CNS endpoint. 2. Pediatric experience in an ICU protocol 3. In addition to RP2D (600 mg/day), all dose levels will be included in all efficacy analyses 4. Patients with dual oncogenic driver not phase 2 eligible 5. Include in Non-evaluable analysis set for consistency
10 Nov 2017	1. Formatting and nomenclature updates 2. Addition of study RXDX-101-14; clarify scope of PK and Healthy Volunteer; ICU Protocol Listings 3. Provide planned sample size by study. 4. Clarification on timing of final analysis including the update at 120 days 5. Expand safety analyses to include laboratory data, ECG, and Weight/BMI 6. Added a section to clarify the basis for Patient Reported Outcome 7. Added a Table of Contents of all planned tables, figures, and listings	1. For consistency with style guide and other documents 2. Planned DDI study in patients will be included in integrated safety analysis; other PK analysis and healthy volunteer safety not in scope of this plan; ICU data to be listed separately 3. Added to clarify protocol vs. integrated analysis sample size goals 4. Specific criteria for final analysis enrollment goal total and length of follow-up time for efficacy analysis population. Additional data cut and analysis (at 120 day) of efficacy and safety. 5. Appropriate to perform these additional safety analyses to complement AE summary 6. Clarification to ensure PRO data are considered for analysis 7. Additional detail to support scope of analysis
10 Aug 2018	1. Formatting and nomenclature updates 2. Remove study RXDX-101-14 3. Add safety analysis subgroups: NTRK, ROS1 NSCLC, Other, and pediatric 4. Clarification of CNS endpoints	1. For consistency with style guides and other documents 2. Study RXDX-101-14 is a DDI study in patients and will be analyzed separately rather than integrated

	5. Clarification of censoring rules for time to event endpoints	3. Subgroups added to represent populations of scientific interest for safety evaluation 4. Distinguish between Time to CNS progression (evaluated in all patients) and Intracranial PFS (evaluated in patients with CNS at baseline) 5. Added a sensitivity analysis to examine impact of start of new anticancer therapy by censoring at last tumor assessment prior to start of new therapy.

Results



BICR=blinded independent central review; ECOG PS= Eastern Cooperative Oncology Group performance status; FU=follow-up; INV=investigator; NSCLC=non-small cell lung cancer; RECIST=Response Evaluation Criteria for Solid Tumors.

Figure 10: Patient populations and analyses sets for patients with ROS1-positive NSCLC supporting the indication

Baseline data

Table 24: Key Demographic and Baseline Disease Characteristics of ROS1 NSCLC Efficacy Evaluable Patients

	Dataset		Primary ROS1 NSCLC Efficacy Evaluable	Complementary ROS1 NSCLC Efficacy Evaluable	Overall ROS1 NSCLC Efficacy Evaluable
	Enrolment cutoff date		**30 April 2017**	**30 April 2017 to 30 November 2017**	**30 November 2017**
			N=53	**N=41**	**N=94**
Demographics	Age	median (range), years	53 (27-73)	53 (33-86)	53 (27-86)
		≥65 years, n (%)	11 (20.8%)	8 (19.5%)	19 (20.2%)
	Sex, n (%)	male	19 (35.8%)	15 (36.6%)	34 (36.2%)
		female	34 (64.2%)	26 (63.4%)	60 (63.8%)
	Race, n (%)	White	31 (58.5%)	15 (36.6%)	46 (48.9%)
		Asian	19 (35.8%)	22 (53.7%)	41 (43.6%)
		Black or African American	3 (5.7%)	2 (4.9%)	5 (5.3%)
		not reported	0	2 (4.9%)	2 (2.1%)
	ECOG PS, n (%)	0	20 (37.7%)	15 (36.6%)	35 (37.2%)
		1	27 (50.9%)	21 (51.2%)	48 (51.1%)
		2	6 (11.3%)	5 (12.2%)	11 (11.7%)
	History of smoking, n (%)		22 (41.5%)	16 (39.0%)	38 (40.4%)
Baseline Disease Characteristics	median time since diagnosis, months (range)		11.5 (0.8-169.2)	4.4 (0.7, 200.4)	7.1 (0.7-200.4)
	Disease stage at initial diagnosis, n (%)		(n=44)	(n=41)	(n=85)
		I (A/B)	2 (4.5%)	3 (7.3%)	5 (5.9%)
		II (A/B	2 (4.5%)	1 (2.4%)	3 (3.5%)
		III (A/B/C)	12 (27.2%)	4 (9.8%)	16 (18.8%)
		IV	27 (61.4%)	33 (80.5%)	60 (70.6%)
		unknown	1 (2.3%)	0	1 (1.2%)
	Metastatic disease	any site, n (%)	52 (98.1%)	41 (100.0%)	93 (98.9%)
		bone, n (%)	20 (37.7%)	17 (41.5%)	37 (39.4%)
		brain, n (%)	23 (43.4%)	17 (41.5%)	40 (42.6%)
		liver, n (%)	8 (15.1%)	10 (24.4%)	18 (19.1%)
		lung, n (%)	38 (71.7%)	16 (39.0%)	54 (57.4%)
		lymph nodes, n (%)	38 (71.7%)	33 (80.5%)	71 (75.5%)
		skin, n (%)	0	1 (2.4%)	1 (1.1%)
		other, n (%)	16 (30.2%)	15 (36.6%)	31 (33.0%)
Previous Cancer Treatment	No of prior systemic therapies[a], n (%)	0	17 (32.1%)	17 (41.5%)	34 (36.2%)
		1	23 (43.4%)	13 (31.7%)	36 (38.2%)
		2	5 (9.4%)	7 (17.1%)	12 (12.8%)
		3	3 (5.7%)	1 (2.4%)	4 (4.3%)
		4	3 (5.7%)	0	3 (3.2%)
		>4	2 (3.8%)	3 (7.3%)	5 (5.3%)
	Previous therapy, n (%)	ny systemic therapy[b]	46 (86.8%)	25 (61.0%)	71 (75.5%)
		surgery	28 (52.8%)	19 (46.3%)	47 (50.0%)
		radiotherapy	24 (45.3%)	14 (34.1%)	38 (40.4%)
	Baseline CNS lesions by INV		**n=23**	**n=17**	**n=40**
	Previous radiotherapy to brain, n (%)		14 (60.9%)	6 (35.3%)	20 (50.0%)

[a] Lines of therapy are determined from the time of metastatic disease diagnosis. Patients may have received other therapies in the adjuvant or neo-adjuvant setting.
[b] Includes any chemotherapy, immunotherapy, targeted therapy or hormonal therapy.

A larger dataset including n=161 patients wth >6 months of follow up has been submitted by the Applicant (enrolled up to 31 Oct 2018, CCOD 1 May 2019). Baseline characteristics of these patients are presented below:

Table 25: Demographic and baseline characteristics, ROS1 NSCLC efficacy evaluable, enrolled up to 31 October 2018 (CCOD: 1 May 2019, DBL: 18 Sept 2019)

	ALKA (N=9)	ST01 (N=7)	ST02 (N=145)	Total (N=161)
Sex				
n	9	7	145	161
Male	2 (22.2%)	3 (42.9%)	52 (35.9%)	57 (35.4%)
Female	7 (77.8%)	4 (57.1%)	93 (64.1%)	104 (64.6%)
Age (years)				
n	9	7	145	161
Mean	53.0	55.4	54.8	54.7
Std	13.0	9.1	12.6	12.5
Median	52.0	57.0	54.0	54.0
Q1, Q3	46.0, 63.0	50.0, 60.0	46.0, 64.0	46.0, 64.0
Min, Max	27, 67	40, 69	20, 86	20, 86
Age group (years)				
n	9	7	145	161
< 65	7 (77.8%)	6 (85.7%)	109 (75.2%)	122 (75.8%)
>= 65	2 (22.2%)	1 (14.3%)	36 (24.8%)	39 (24.2%)
Age Group (years)				
n	9	7	145	161
18-<75	9 (100.0%)	7 (100.0%)	138 (95.2%)	154 (95.7%)
>=75	0	0	7 (4.8%)	7 (4.3%)
Ethnicity				
n	0	7	144	151
Hispanic or Latino	0	0	4 (2.8%)	4 (2.6%)
Not Hispanic or Latino	0	5 (71.4%)	132 (91.7%)	137 (90.7%)
Not Stated	0	1 (14.3%)	2 (1.4%)	3 (2.0%)
Unknown	0	1 (14.3%)	6 (4.2%)	7 (4.6%)
Race				
n	9	7	145	161
Asian	1 (11.1%)	4 (57.1%)	68 (46.9%)	73 (45.3%)
Black or African American	0	0	7 (4.8%)	7 (4.3%)
White	8 (88.9%)	3 (42.9%)	60 (41.4%)	71 (44.1%)
Other	0	0	2 (1.4%)	2 (1.2%)
Not Reported	0	0	8 (5.5%)	8 (5.0%)
Weight (kg)				
n	9	7	145	161
Mean	61.22	69.41	68.68	68.29
Std	11.77	18.85	16.54	16.42
Median	57.00	68.00	67.00	66.00
Q1, Q3	53.50, 63.50	54.90, 90.60	57.00, 78.50	55.90, 78.35
Min, Max	49.0, 86.0	47.2, 97.5	38.5, 115.9	38.5, 115.9
Height (cm)				
n	9	7	145	161
Mean	163.11	165.34	163.96	163.97
Std	10.26	9.65	9.73	9.70
Median	160.00	160.10	163.50	163.00
Q1, Q3	160.00, 168.00	157.10, 173.30	156.80, 170.00	157.10, 170.00
Min, Max	144.0, 179.0	157.0, 182.0	142.0, 192.0	142.0, 192.0
BSA (m2)				
n	9	7	145	161
Mean	1.66	1.76	1.76	1.75
Std	0.17	0.28	0.24	0.24
Median	1.66	1.71	1.73	1.73
Q1, Q3	1.56, 1.68	1.55, 2.05	1.57, 1.92	1.56, 1.91
Min, Max	1.5, 2.1	1.5, 2.2	1.3, 2.5	1.3, 2.5
BMI (kg/m^2)				
n	9	7	145	161
Mean	23.25	24.97	25.38	25.25
Std	5.44	4.07	5.04	5.02
Median	21.48	25.17	24.35	24.22
Q1, Q3	19.05, 24.80	21.72, 29.43	22.23, 27.62	22.05, 27.39
Min, Max	17.4, 35.2	19.1, 30.2	15.5, 45.7	15.5, 45.7
ECOG				
n	9	7	145	161
0	3 (33.3%)	2 (28.6%)	61 (42.1%)	66 (41.0%)
1	6 (66.7%)	4 (57.1%)	69 (47.6%)	79 (49.1%)
2	0	1 (14.3%)	15 (10.3%)	16 (9.9%)
History of Smoking				
n	9	7	145	161
No	6 (66.7%)	6 (85.7%)	89 (61.4%)	101 (62.7%)
Yes	3 (33.3%)	1 (14.3%)	56 (38.6%)	60 (37.3%)
Current	1 (33.3%)	0	6 (10.7%)	7 (11.7%)
Former	2 (66.7%)	1 (100.0%)	50 (89.3%)	53 (88.3%)

Table 26: Disease characteristics and history, ROS1 NSCLC efficacy evaluable, enrolled up to 31 October 2018 (CCOD: 1 May 2019, DBL: 18 Sept 2019)

	ALKA (N=9)	ST01 (N=7)	ST02 (N=145)	Total (N=161)
Primary Diagnosis				
n	9	7	145	161
NSCLC	9 (100.0%)	7 (100.0%)	145 (100.0%)	161 (100.0%)
Histology				
n	9	7	145	161
ADENOCARCINOMA	7 (77.8%)	7 (100.0%)	142 (97.9%)	156 (96.9%)
ADENOSQUAMOUS CARCINOMA	0	0	1 (0.7%)	1 (0.6%)
BRONCHIOLOALVEOLAR CARCINOMA	0	0	1 (0.7%)	1 (0.6%)
NSCLC - NOS	2 (22.2%)	0	1 (0.7%)	3 (1.9%)
Time Since Diagnosis (Months)				
n	0	7	145	152
Mean	NE	22.21	19.65	19.77
Std	NE	24.26	31.45	31.10
Median	NE	20.30	6.90	6.95
Q1, Q3	NE	1.00, 39.50	1.80, 20.60	1.80, 21.90
Min, Max	NE - NE	0.8, 66.0	0.7, 200.4	0.7, 200.4
Stage at Initial Diagnosis				
n	0	7	145	152
IA	0	0	3 (2.1%)	3 (2.0%)
IB	0	0	3 (2.1%)	3 (2.0%)
IIA	0	0	3 (2.1%)	3 (2.0%)
IIB	0	1 (14.3%)	5 (3.4%)	6 (3.9%)
III	0	3 (42.9%)	0	3 (2.0%)
IIIA	0	0	11 (7.6%)	11 (7.2%)
IIIB	0	0	8 (5.5%)	8 (5.3%)
IIIC	0	0	2 (1.4%)	2 (1.3%)
IV	0	3 (42.9%)	108 (74.5%)	111 (73.0%)
UNKNOWN	0	0	2 (1.4%)	2 (1.3%)
Extent of Disease				
n	9	7	145	161
LOCALLY ADVANCED	0	0	3 (2.1%)	3 (1.9%)
METASTATIC DISEASE	9 (100.0%)	7 (100.0%)	142 (97.9%)	158 (98.1%)
Metastatic Sites				
Bone	1 (11.1%)	3 (42.9%)	56 (38.6%)	60 (37.3%)
Brain	2 (22.2%)	3 (42.9%)	48 (33.1%)	53 (32.9%)
Liver	0	0	26 (17.9%)	26 (16.1%)
Lung	9 (100.0%)	6 (85.7%)	66 (45.5%)	81 (50.3%)
Lymph Nodes	7 (77.8%)	4 (57.1%)	101 (69.7%)	112 (69.6%)
Skin	0	0	1 (0.7%)	1 (0.6%)
Other	5 (55.6%)	1 (14.3%)	53 (36.6%)	59 (36.6%)

Patients may have multiple sites of metastases at baseline.

Table 27: Previous cancer treatments, ROS1 NSCLC efficacy evaluable, enrolled up to 31 October 2018 (CCOD: 1 May 2019, DBL: 18 Sept 2019)

	ALKA (N=9)	ST01 (N=7)	ST02 (N=145)	Total (N=161)
Any previous therapy	9 (100.0%)	5 (71.4%)	101 (69.7%)	115 (71.4%)
Any chemotherapy	9 (100.0%)	4 (57.1%)	97 (66.9%)	110 (68.3%)
Any Immunotherapy	0	0	24 (16.6%)	24 (14.9%)
Any targeted therapy	2 (22.2%)	1 (14.3%)	11 (7.6%)	14 (8.7%)
Any hormonal therapy	0	0	1 (0.7%)	1 (0.6%)
Prior lines of therapy				
n	9	7	145	161
0	0	3 (42.9%)	57 (39.3%)	60 (37.3%)
1	4 (44.4%)	3 (42.9%)	57 (39.3%)	64 (39.8%)
2	3 (33.3%)	0	15 (10.3%)	18 (11.2%)
3	2 (22.2%)	0	4 (2.8%)	6 (3.7%)
4	0	1 (14.3%)	4 (2.8%)	5 (3.1%)
>4	0	0	8 (5.5%)	8 (5.0%)
Any previous radiotherapy	3 (33.3%)	3 (42.9%)	51 (35.2%)	57 (35.4%)
Any previous surgeries	2 (22.2%)	5 (71.4%)	76 (52.4%)	83 (51.6%)

Numbers analysed

Table 28: Patient Disposition for Study, ROS1 NSCLC Efficacy Evaluable enrolled up to APR 30, 2017, CCOD MAY 31 2018

	ALKA (N=9)	ST01 (N=7)	ST02 (N=37)	Total (N=53)
Study Status				
Completed	4 (44.4%)	0	0	4 (7.5%)
Ongoing	1 (11.1%)	2 (28.6%)	23 (62.2%)	26 (49.1%)
Discontinued	4 (44.4%)	5 (71.4%)	14 (37.8%)	23 (43.4%)
Death	1 (25.0%)	0	8 (57.1%)	9 (39.1%)
Informed Consent Withdrawn	0	0	6 (42.9%)	6 (26.1%)
Withdrawal By Subject	0	2 (40.0%)	0	2 (8.7%)
Other	3 (75.0%)	3 (60.0%)	0	6 (26.1%)

Table 29: Patient Disposition for Entrectinib Treatment, ROS1 NSCLC Efficacy Evaluable enrolled up to APR 30, 2017, CCOD MAY 31 2018

	ALKA (N=9)	ST01 (N=7)	ST02 (N=37)	Total (N=53)
Discontinued Treatment	8 (88.9%)	5 (71.4%)	19 (51.4%)	32 (60.4%)
Adverse Event	1 (12.5%)	1 (20.0%)	3 (15.8%)	5 (15.6%)
Informed Consent Withdrawn	0	0	2 (10.5%)	2 (6.3%)
Progressive Disease	7 (87.5%)	4 (80.0%)	14 (73.7%)	25 (78.1%)

At the updated cut-off date of 31 Oct 2018, a total of 17 subjects (32.1%) (1 in ALKA; 2 in STARTRK-1 and 14 in STARTRK-2) were still on treatment.

Outcomes and estimation

Table 30: Overview of efficacy results of Entrectinib in adult patients with ROS1-Positive NSCLC as assessed by BICR

	Original submission		D180 responses		
	ROS1 NSCLC Efficacy Evaluable Primary Dataset	**ROS1 NSCLC Dataset regardless of follow-up time**	**ROS1 NSCLC Efficacy Evaluable Primary Dataset**	**complementary ROS1 NSCLC (Complementary Dataset)**	**ROS1 NSCLC Dataset regardless of follow-up time**
Enrolment cutoff date	30 April 2017	30 November 2017	30 April 2017	30 April 2017 to 30 November 2017	30 November 2017
Clinical cut-off date	31 May 2018	31 May 2018	1 May 2019	1 May 2019	1 May 2019
Total no. of patients enrolled	**N=53**	**N=94**	**N=53**	**N=41**	**N=94**
Duration of follow-up, median (95% CI)[a]	15.54 (14.75, 19.02)	12.2 (10.18, 14.62)	25.4 (23.2, 28.4)	18.9 (16.8, 19.8)	20.3 (19.2, 22.8)
Objective Response (ORR)[b]					
Patients with confirmed CR or PR, n	41	68	42	27	69
ORR, % (95% CI)[c]	77.4% (63.79, 87.72)	72.3% (62.15, 81.07)	79.2% (65.9, 89.2)	65.9% (49.4, 79.9)	73.4% (63.3, 82.0)
Best Overall Response (BOR)[b]					
Complete Response, n (%)	3 (5.7%)	7 (7.4%)	5 (9.4%)	6 (14.6%)	11 (11.7%)
Partial Response, n (%)	38 (71.7%)	61 (64.9%)	37 (69.8%)	21 (51.2%)	58 (61.7%)
Stable Disease, n (%)	1 (1.9%)	7 (7.4%)	1 (1.9%)	5 (12.2%)	6 (6.4%)
Progressive Disease, n (%)	4 (7.5%)	7 (7.4%)	4 (7.5%)	4 (9.8%)	8 (8.5%)
Non CR/PD, n (%)	3 (5.7%)	4 (4.3%)	2 (3.8%)	1 (2.4%)	3 (3.2%)
Missing or unevaluable, n (%)	4 (7.5%)	8 (8.5%)	4 (7.5%)	4 (9.8%)	8 (8.5%)
Duration of Response (DOR)[b]					
Patients with event, n (%)	19/41 (46.3%)	25/68 (36.8%)	22/42 (52.4%)	14/27 (51.9%)	36/69 (52.2%)
Median, months (95% CI)[a]	24.6 (11.4, 34.8)	15.7 (12.6, 34.8)	20.5 (12.6, 34.8)	16.5 (11.1, NE)	16.5 (14.6, 28.6)
Event-free probability (95% CI)[a]					
6 months[d]	0.82 (0.70, 0.94)	0.79 (0.69, 0.89)	0.82 (0.70, 0.94)	0.81 ((0.67, 0.96)	0.82 (0.72, 0.91)
12 months[d]	0.65 (0.49, 0.81)	0.65 (0.51, 0.78)	0.66 (0.51, 0.81)	0.66 (0.48, 0.84)	0.66 (0.54, 0.78)
Secondary Endpoints					
Clinical Benefit Rate (CBR)[b]	41	Not provided	42	28	70
CBR (95% CI)[c]	77.4% (63.8, 87.7)	Not provided	79.2% (65.9, 89.2)	68.3% (51.9, 81.9)	74.5% (64.4, 82.9)
Progression-Free Survival (PFS)[b]					
Patients with event, n (%)	25 (47.2%)	40 (42.6%)	30 (56.6%)	24 (58.5%)	54 (57.4%)
Median, months (95% CI)[a]	19.0 (12.2, 36.6)	16.8 (12.2, 29.6)	19.0 (12.2, 29.6)	15.5 (6.4, 21.1)	16.8 (12.0, 21.4)
Time to CNS Progression[b]					
Median, months (95% CI)[a]	NE (15.1, NE)	Not provided	25.6 (15.1, NE)	NE (15.7, NE)	24.8 (16.1, NE)
Overall Survival (OS)					
Patients with event, n (%)	9 (17%)	Not provided	14 (26.4%)	11 (26.8%)	25 (26.6%)
Median, months (95% CI)[a]	NE (NE, NE)	Not provided	NE (28.3, NE)	NE (NE, NE)	NE (28.3, NE)

NE, not estimable.

[a] Median and percentiles for time-to-event analyses based on Kaplan-Meier estimates. Confidence Intervals (CI) for the median were computed using the method of Brookmeyer and Crowley.

[b] by RECIST v1.1.

[c] 95% CIs for proportions calculated using the Clopper-Pearson method.

[d] Event-Free Probabilities are Kaplan-Meier estimates and confidence intervals were calculated using the method of Kalbfleisch and Prentice

Table 31: overview of intracranial efficacy results of Entrectinib in adult patients with ROS1-Positive NSCLC and CNS disease at baseline as assessed by BICR

	Original MAA		**D180 responses**		
	ROS1 NSCLC Efficacy Evaluable Primary Dataset	**ROS1 NSCLC Dataset regardless of follow-up time**	**ROS1 NSCLC Efficacy Evaluable Primary Dataset**	**complementary ROS1 NSCLC (Complementary Dataset)**	**ROS1 NSCLC Dataset regardless of follow-up time**
enrollment cutoff date for patients included	30 April 2017	30 November 2017	30 April 2017	30 April 2017 to 30 November 2017	30 November 2017
clinical cutoff date for analysis	31 May 2018	31 Oct 2018	1 May 2019	1 May 2019	1 May 2019
Total no. of patients enrolled	**N=53**	**N=94**	**N=53**	**N=41**	**N=94**
Patients with CNS Metastases at Baseline by BICR*	**(N=20)**	**(n=35)**	**(N=20)**	**(N=14)**	**(N=34)**
Intracranial ORR[b]					
Responders (CR or PR),n	11	17	11	6	17
IC-ORR, % (95% CI)[c]	55.0% (31.5, 76.9)	48.6% (31.4, 66.0)	55.0% (31.5, 76.9)	42.9% (17.7, 71.1)	50.0% (32.4, 67.6)
Intracranial DOR					
No. of patients with events, n (% of responders)	5/11 (45.5%)	7/17 (41.2%)	7/11 (63.6%)	4/6 (66.7%)	11/17 (64.7%)
Median, months(95% CI)[c]	12.9 (5.6, NE)	12.9 (5.6, NE)	12.9 (5.6, NE)	12.9 (3.7, NE)	12.9 (5.6, 22.1)
Intracranial PFS					
No. of patients with events, n (%)	13 (65.5%)	Not provided	15 (75.0%)	10 (71.4%)	25 (73.5%)
Median, months(95% CI)[a]	7.7 (3.8, 19.3)	Not provided	7.7 (3.8, 13.6)	13.8 (2.7, 17.4)	7.7 (4.6, 15.7)

A larger dataset including n=161 patients wth has been submitted by the Applicant as per CHMP request. This dataset include ROS1 NSCLC adult patients enrolled up to 31 Oct 2018, with CCOD 1 May 2019, i.e. all subjects had >6 months of follow up.

Median survival follow up is 15.8 months (95%CI 14.49, 18.23).

The efficacy results of this n=161 updated dataset are below:

- ORR 67.1% (responders 108/161) (95%CI 59.25, 74.27); CR 14 (8.7%), PR 94 (58.4%), SD 14 (8.7%), PD 15 (9.3%), non CR/PD 10 (6.2%), missing or unevaluable 14 (8.7%).

- DOR median 15.7 months (95%CI 13.9, 28.6); patients with DOR event 44.4% (48/108)

- PFS median 15.7 months (95%CI 11.0, 21.1); patients with PFS event 50.9% (82/161)

- OS median NE (95%CI 28.3, NE); patients with OS event 23.6% (38/161)

Of those 161 subjects, 46 had CNS disease at baseline. IC-ORR was 52.2% (24/46) (95%CI 36.95, 67.1), which includes 8 CR (17.4%). Of those, 24 had measurable CNS disease by BIRC, in whom IC-ORR was 79.2% (19 responders) (95%CI 57.85, 92.9); IC-DOR in the 19 responders was 12.9 months (95%CI 6.8, 22.1).

Primary endpoints

ORR

Table 32: Objective response and best overall response (investigator assessment), ROS1 NSCLC efficacy evaluable enrolled up to 30 November 2017

	ALKA (N=9)	ST01 (N=7)	ST02 (N=78)	Total (N=94)
Responders	7 (77.8%)	6 (85.7%)	56 (71.8%)	69 (73.4%)
Non-Responders	2 (22.2%)	1 (14.3%)	22 (28.2%)	25 (26.6%)
95% CI for Response Rates	(39.99, 97.19)	(42.13, 99.64)	(60.47, 81.41)	(63.29, 81.99)
Complete Response (CR)	2 (22.2%)	2 (28.6%)	3 (3.8%)	7 (7.4%)
Partial Response (PR)	5 (55.6%)	4 (57.1%)	53 (67.9%)	62 (66.0%)
Stable Disease (SD)	0	0	7 (9.0%)	7 (7.4%)
Progressive Disease (PD)	2 (22.2%)	0	8 (10.3%)	10 (10.6%)
Non CR/PD	0	0	0	0
Missing or unevaluable	0	1 (14.3%)	7 (9.0%)	8 (8.5%)

Best Overall Response is derived per RECIST 1.1. Not Evaluable/Not Done category includes patients having on-study scans that could not be evaluated and patients who discontinued prior to obtaining adequate scans to evaluate or confirm response. SD and NonCR/NonPD must be observed study day 35 or later, otherwise they count as NE. Objective response is defined as PR or CR confirmed by repeat-imaging at least 28 days following first documentation of response. Otherwise, the patient is considered to be a non-responder. Confidence Intervals (CI) are calculated using the Clopper-Pearson method.

CCOD: 01 May 2019, DBL: 18 September 2019

In a group of n=161 patients with a clinical cut-off of 1 May 2019, but with at least 6 months of FU (and not 12 months as above), results are shown below:

Table 33: Objective Response and Best Overall Response (BICR Assessment) for ROS1 NSCLC patients with at least 6 months of follow-up

Overall Efficacy: Objective Response and Best Overall Response (BICR Assessment), Enrolled up to Oct 31, 2018, ROS1 NSCLC Efficacy Evaluable
Protocols: GO40782, GO40783, GO40784
CCOD: May 01 2019, DBL: Sep 18 2019

	ALKA (N=9)	ST01 (N=7)	ST02 (N=145)	Total (N=161)
Responders	7 (77.8%)	6 (85.7%)	95 (65.5%)	108 (67.1%)
Non-Responders	2 (22.2%)	1 (14.3%)	50 (34.5%)	53 (32.9%)
95% CI for Response Rates	(39.99, 97.19)	(42.13, 99.64)	(57.18, 73.21)	(59.25, 74.27)
Complete Response (CR)	2 (22.2%)	0	12 (8.3%)	14 (8.7%)
Partial Response (PR)	5 (55.6%)	6 (85.7%)	83 (57.2%)	94 (58.4%)
Stable Disease (SD)	1 (11.1%)	0	13 (9.0%)	14 (8.7%)
Progressive Disease (PD)	1 (11.1%)	0	14 (9.7%)	15 (9.3%)
Non CR/PD	0	0	10 (6.9%)	10 (6.2%)
Missing or unevaluable	0	1 (14.3%)	13 (9.0%)	14 (8.7%)

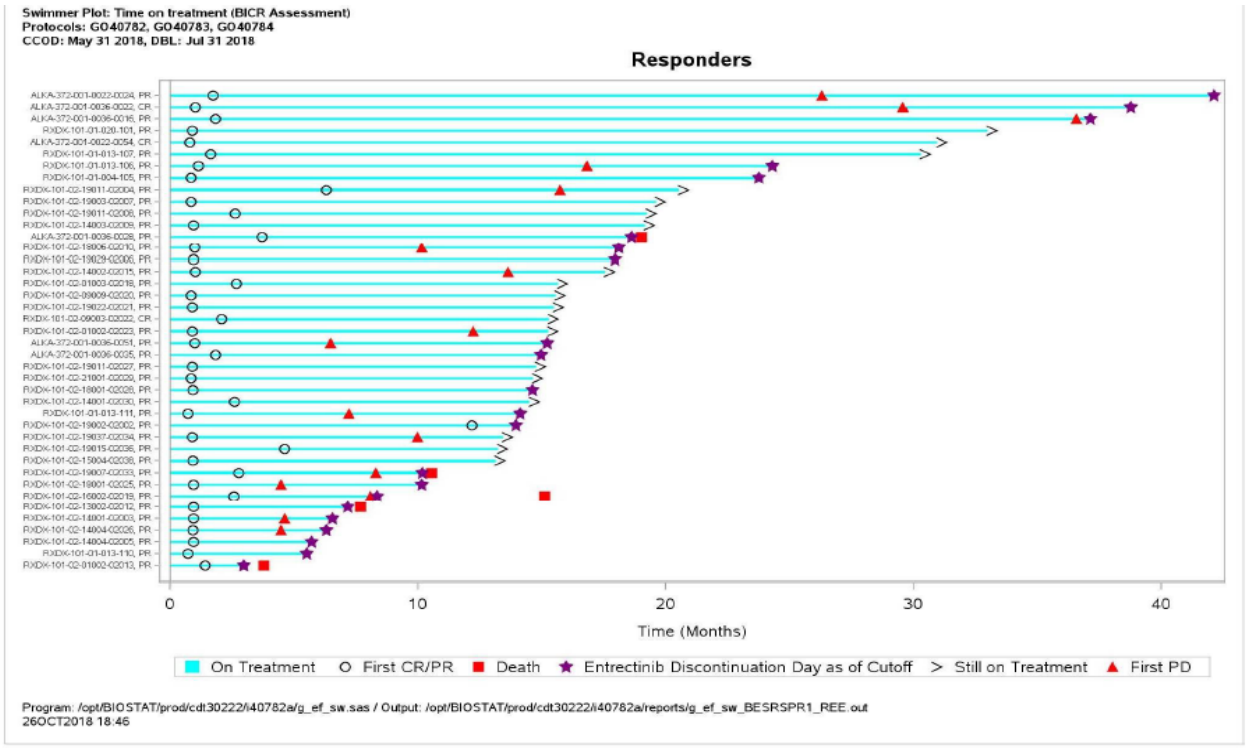
Best Overall Response is derived per RECIST 1.1. Not Evaluable/Not Done category includes patients having on-study scans that could not be evaluated and patients who discontinued prior to obtaining adequate scans to evaluate or confirm response. SD and NonCR/NonPD must be observed study day 35 or later, otherwise they count as NE. Objective response is defined as PR or CR confirmed by repeat- imaging at least 28 days following first documentation of response. Otherwise, the patient is considered to be a non-responder.
Confidence Intervals (CI) are calculated using the Clopper-Pearson method.

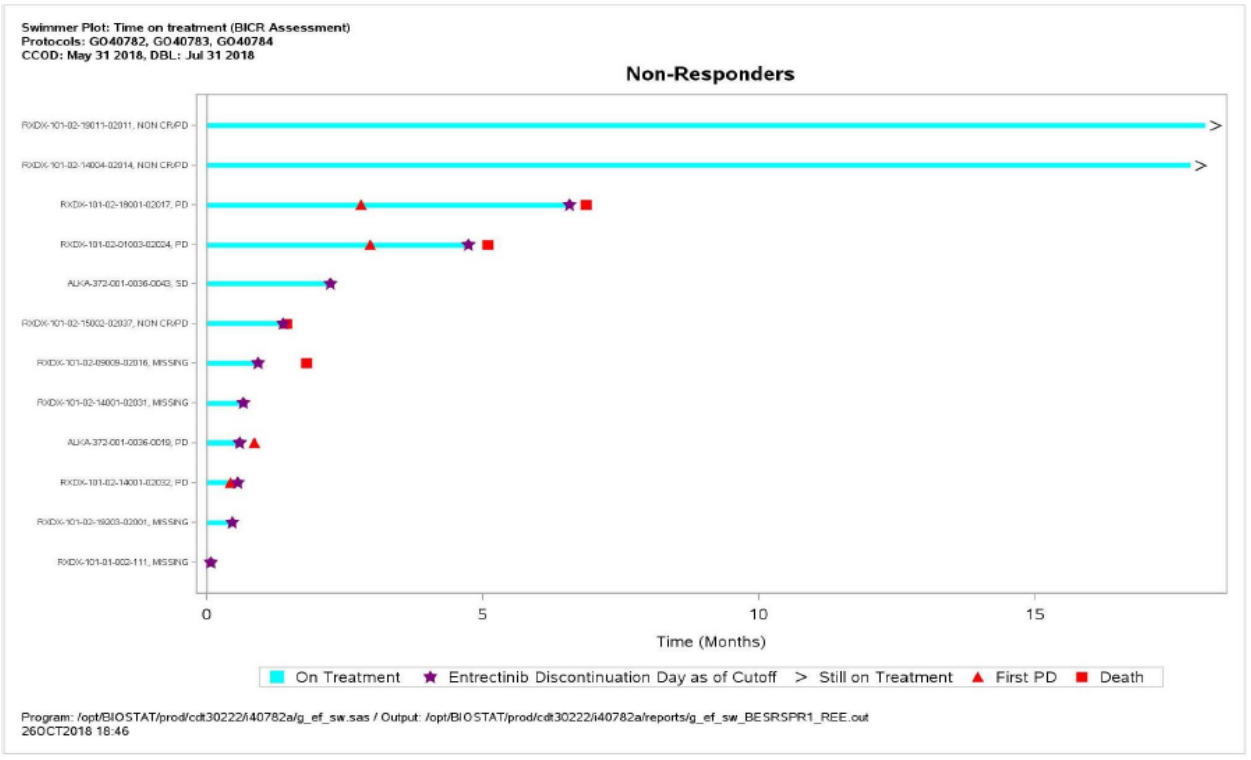
DOR

Table 34: Duration of Response (BICR Assessment), ROS1 NSCLC Efficacy Evaluable Analysis Set, enrolled up to APR 30, 2017. CCOD: May 31 2018

	ALKA (N=7)	ST01 (N=6)	ST02 (N=28)	Total (N=41)
Patients included in analysis	7 (100.0%)	6 (100.0%)	28 (100.0%)	41 (100.0%)
Patients with event (%)	5 (71.4%)	2 (33.3%)	12 (42.9%)	19 (46.3%)
Earliest contributing event				
Disease Progression	4	2	10	16
Death	1	0	2	3
Patients without event (%)	2 (28.6%)	4 (66.7%)	16 (57.1%)	22 (53.7%)
Time to event (months)				
Median	28.6	NE	NE	24.6
95% CI for Median	(15.3, 34.8)	(6.5, NE)	(9.2, NE)	(11.4, 34.8)
25% and 75%-ile	15.3, 34.8	15.7, NE	6.8, NE	9.1, 34.8
Range	5.5 to 34.8	4.7* to 31.3*	1.8* to 18.4*	1.8* to 34.8
6 Months				
Patients remaining at risk	6	5	20	31
Event free probability	0.86	1.00	0.77	0.82
95% CI	(0.60, 1.00)	(1.00, 1.00)	(0.61, 0.93)	(0.70, 0.94)
9 Months				
Patients remaining at risk	6	4	18	28
Event free probability	0.86	0.80	0.73	0.77
95% CI	(0.60, 1.00)	(0.45, 1.00)	(0.56, 0.90)	(0.63, 0.90)
12 Months				
Patients remaining at risk	5	3	10	18
Event free probability	0.86	0.80	0.56	0.65
95% CI	(0.60, 1.00)	(0.45, 1.00)	(0.36, 0.76)	(0.49, 0.81)
18 Months				
Patients remaining at risk	4	2	1	7
Event free probability	0.69	0.53	0.50	0.50
95% CI	(0.32, 1.00)	(0.05, 1.00)	(0.30, 0.71)	(0.31, 0.70)

Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.





BICR=blinded independent central review; CCOD=clinical cut-off date; CR=complete response; DBL=database lock; NSCLC=non-small cell lung cancer; PD=progressive disease; PR=partial response.

Figure 11: Swimmer Plot: Time on Treatment (BICR Assessment), ROS1 NSCLC Efficacy Evaluable Analysis Set (responders n=41; non responders n=12), CCOD 31 May 2018

Table 35: Duration of response (BICR Assessment) for ROS1 NSCLC patients with at least 6 months of follow-up

Kaplan-Meier Event-Free Rates for Duration of Response (BICR Assessment), Enrolled up to Oct 31, 2018, ROS1 NSCLC Efficacy Evaluable
Protocols: GO40782, GO40783, GO40784
CCOD: May 01 2019, DBL: Sep 18 2019

	ALKA (N=7)	ST01 (N=6)	ST02 (N=95)	Total (N=108)
Patients included in analysis	7 (100.0%)	6 (100.0%)	95 (100.0%)	108 (100.0%)
Patients with event (%)	5 (71.4%)	2 (33.3%)	41 (43.2%)	48 (44.4%)
Earliest contributing event				
Disease Progression	4	2	30	36
Death	1	0	11	12
Patients without event (%)	2 (28.6%)	4 (66.7%)	54 (56.8%)	60 (55.6%)
Time to event (months)				
Median	28.6	NE	14.9	15.7
95% CI for Median	(15.3, 34.8)	(6.5, NE)	(11.4, NE)	(13.9, 28.6)
25% and 75%-ile	15.3, 34.8	15.7, NE	8.9, NE	9.1, 34.8
Range	5.5 to 38.7*	4.7* to 42.3*	1.8* to 27.6*	1.8* to 42.3*
6 Months				
Patients remaining at risk	6	5	65	76
Event free probability	0.86	1.00	0.82	0.83
95% CI	(0.60, 1.00)	(1.00, 1.00)	(0.74, 0.90)	(0.76, 0.90)
9 Months				
Patients remaining at risk	6	4	57	67
Event free probability	0.86	0.80	0.74	0.75
95% CI	(0.60, 1.00)	(0.45, 1.00)	(0.65, 0.83)	(0.67, 0.84)
12 Months				
Patients remaining at risk	5	3	37	45
Event free probability	0.86	0.80	0.59	0.63
95% CI	(0.60, 1.00)	(0.45, 1.00)	(0.48, 0.71)	(0.53, 0.73)
18 Months				
Patients remaining at risk	4	2	15	21
Event free probability	0.69	0.53	0.46	0.48
95% CI	(0.32, 1.00)	(0.05, 1.00)	(0.33, 0.58)	(0.36, 0.59)

* Censored
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Secondary endpoints

Time to CNS Progression

The median time to first documentation of radiographic CNS disease progression or death due to any cause as assessed by BICR was not estimable (NE) (95% CI: 15.1, NE) in the original MAA (CCOD 31 May 2018). In the updated analysis (CCOD 31 October 2018) was 30.8 months (95% CI: 15.1, NE).

Progression Free Survival

Table 36: Kaplan-Meier Event-Free Rates for Progression-Free Survival (BICR Assessment), ROS1 NSCLC Efficacy Evaluable Analysis Set, enrolled up to APR 30, 2017. CCOD: May 31 2018

	ALKA (N=9)	ST01 (N=7)	ST02 (N=37)	Total (N=53)
Patients with event (%)	6 (66.7%)	2 (28.6%)	17 (45.9%)	25 (47.2%)
Earliest contributing event				
Disease Progression	5	2	13	20
Death	1	0	4	5
Patients without event (%)	3 (33.3%)	5 (71.4%)	20 (54.1%)	28 (52.8%)

Time to event (months)				
Median	26.3	NE	15.7	19.0
95% CI for Median	(6.5, 36.6)	(7.2, NE)	(8.3, NE)	(12.2, 36.6)
25% and 75%-ile	19.0, 36.6	16.8, NE	4.6, NE	7.7, 36.6
Range	0.9 to 36.6	0.0* to 32.2*	0.0* to 19.3*	0.0* to 36.6
6 Months				
Patients remaining at risk	7	5	25	37
Event free probability	0.89	1.00	0.74	0.80
95% CI	(0.68, 1.00)	(1.00, 1.00)	(0.60, 0.89)	(0.68, 0.91)
9 Months				
Patients remaining at risk	6	4	22	32
Event free probability	0.76	0.80	0.65	0.69
95% CI	(0.47, 1.00)	(0.45, 1.00)	(0.49, 0.81)	(0.56, 0.82)
12 Months				
Patients remaining at risk	6	3	19	28
Event free probability	0.76	0.80	0.59	0.65
95% CI	(0.47, 1.00)	(0.45, 1.00)	(0.43, 0.76)	(0.51, 0.78)
18 Months				
Patients remaining at risk	5	2	1	8
Event free probability	0.76	0.53	0.45	0.52
95% CI	(0.47, 1.00)	(0.05, 1.00)	(0.25, 0.65)	(0.36, 0.68)

Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.

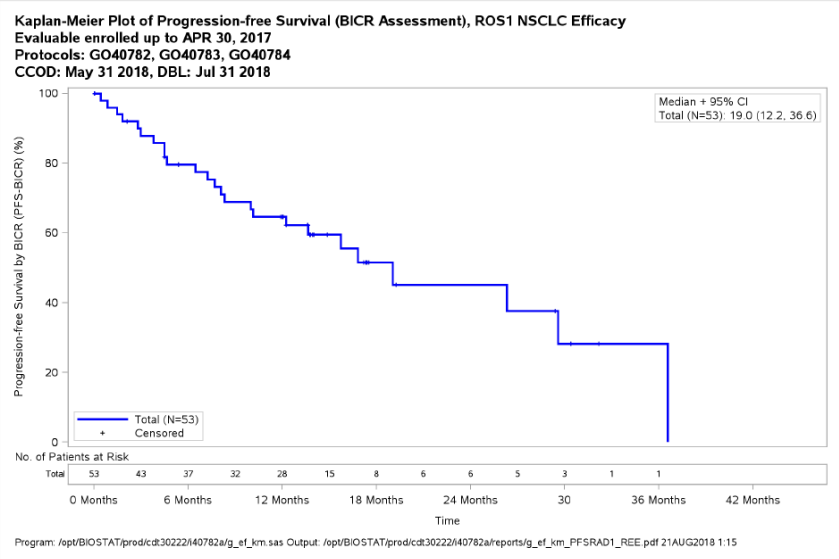


Figure 12: Kaplan-Meier plot of Progression-Free Survival (BICR Assessment), ROS1 NSCLC Efficacy Evaluable Analysis Set (CCOD 31 May 2018)

First site of progression: first progression occurred intracranially in 36% (8/22) of subjects who progressed during the study. Higher incidence of progression in the brain as 1st site was observed in patient with baseline CNS disease (65%, 6/9) compared to patients with no baseline CNS disease (15%, 2/13).

Among the patients responding to entrectinib and then progressed while on study (n=18), in 16% of subjects (3/18) the first site of progression was the brain. Higher incidence of progression in the brain as 1st site was observed in patient with baseline CNS disease (33%, 2/6) compared to patients with no baseline CNS disease (8%, 1/12).

Overall Survival

Table 37: Kaplan-Meier Event-Free Rates for Overall Survival, ROS1 NSCLC Efficacy Evaluable Analysis Set, enrolled up to APR 30, 2017. CCOD: May 31 2018

	ALKA (N=9)	ST01 (N=7)	ST02 (N=37)	Total (N=53)
Patients with event (%)	1 (11.1%)	0	8 (21.6%)	9 (17.0%)
Earliest contributing event				
Death	1	0	8	9
Patients without event (%)	8 (88.9%)	7 (100.0%)	29 (78.4%)	44 (83.0%)
Time to event (months)				
Median	NE	NE	NE	NE
95% CI for Median	(19.0, NE)	NE	NE	NE
25% and 75%-ile	NE	NE	15.1, NE	NE
Range	0.9* to 43.1*	1.7* to 32.2*	0.8* to 25.3*	0.8* to 43.1*
6 Months				
Patients remaining at risk	7	5	30	42
Event free probability	1.00	1.00	0.89	0.92
95% CI	(1.00, 1.00)	(1.00, 1.00)	(0.78, 0.99)	(0.84, 1.00)
9 Months				
Patients remaining at risk	7	5	26	38
Event free probability	1.00	1.00	0.82	0.87
95% CI	(1.00, 1.00)	(1.00, 1.00)	(0.69, 0.95)	(0.78, 0.97)
12 Months				
Patients remaining at risk	7	5	24	36
Event free probability	1.00	1.00	0.79	0.85
95% CI	(1.00, 1.00)	(1.00, 1.00)	(0.65, 0.93)	(0.74, 0.95)
18 Months				
Patients remaining at risk	5	4	9	18
Event free probability	1.00	1.00	0.74	0.82
95% CI	(1.00, 1.00)	(1.00, 1.00)	(0.59, 0.90)	(0.70, 0.93)

Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.

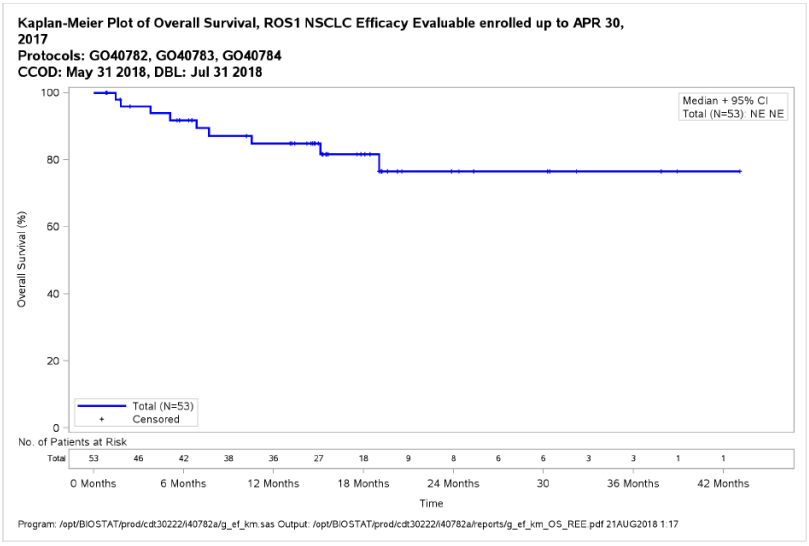


Figure 13: Kaplan-Meier plot of Overall Survival, ROS1 NSCLC Efficacy Evaluable Analysis Set (CCOD 31 May 2018)

Intracranial-specific objective response endpoints

Systemic efficacy by baseline CNS disease status

Table 38: Summary of Efficacy of Entrectinib (BICR Assessment) by Baseline CNS Disease Status (ROS1 NSCLC Efficacy Evaluable Analysis Set (ECOD: 30 November 2017, CCOD: 1 May 2019)

	ROS1 NSCLC Efficacy Evaluable Primary Dataset	
Enrolment cut-off date	**30 November 2017**	
Total no. of patients enrolled	**N=94**	
	Baseline CNS Disease Status[d]	
	No (N=60)	**Yes (N=34)**
Primary Endpoints		
Objective Response Rate (ORR)[a]		
No. of patients with confirmed CR or PR, n	46	23
ORR, % (95% CI)[b]	76.7% (64.0%, 86.6%)	67.6% (49.5%, 82.6%)
Best Overall Response (BOR)		
Complete Response, n (%)	8 (13.3%)	3 (8.8%)
Partial Response, n (%)	38 (63.3%)	20 (58.8%)
Stable Disease, n (%)	4 (6.7%)	2 (5.9%)
Progressive Disease, n (%)	3 (5.0%)	5 (14.7%)
non CR/non-PD, n (%)	3 (5.0%)	0
Missing or unevaluable, n (%)	4 (6.7%)	4 (11.8%)
Duration of Response (DOR)[a]		
No. of patients with events/no. of responders (%)	23/46 (50.0%)	13/23 (56.5%)
Median, months (95% CI)[c]	24.6 (13.9, NE)	14.9 (9.2, 20.5)
Secondary Endpoints		
Clinical Benefit Rate (CBR)[a]		
No of patients with confirmed CR or PR, or SD ≥6 months	47	23
CBR, % (95% CI)[b]	78.3% (65.8%, 87.9%)	67.6% (49.5%, 82.6%)
Progression-Free Survival[a]		
No. of patients with event, n (%)	32 (53.3%)	22 (64.7%)
Median, months (95% CI)[c]	21.1 (14.8, 30.8)	9.9 (4.6, 17.4)
Overall Survival		
No. of patients with event, n (%)	13 (21.7%)	12 (35.3%)
Median, months (95% CI)[c]	NE (30.8, NE)	28.3 (16.1, NE)

NE, not estimable.

[a] All endpoints based on tumor response and progression were by blinded independent central review (BICR) as per RECIST v1.1 criteria.

[b] Confidence Intervals (CI) calculated using the Clopper-Pearson method.

[c] Median and percentiles based on Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.

[d] CNS metastatic status at baseline as determined by the BICR.

Intracranial efficacy in patients with CNS disease at baseline

Table 39: **Intracranial ORR and Duration of Intracranial Response (BICR Assessment) by Prior Brain Radiation Therapy Status in Patients with ROS1-Positive NSCLC and CNS Disease at Baseline (CCOD: 1 May 2019)**

	Measureable Disease	Measureable + Non Measureable Disease
	N=18	N=34
Intracranial ORR[a], n (%) (95% CI)[b]		
No. patients included in analysis		
Responders (PR or CR) (%) (95% CI)[b]		
Total	n=18	n=34
	14 (77.8%) (52.4%, 93.6%)	17 (50.0%) (32.4%, 67.6%)
Brain radiation status and timing relative to study entry		
No brain RT	n=9	n=17
	7 (77.8%) (40.0%, 97.2%)	8 (47.1%) (23.0%, 72.2%)
≤2 months	n=8	n=12
	7 (87.5%) (47.4%, 99.7%)	9 (75.0%) (42.8%, 94.5%)
>2 months	n=1	n=5
	0 (0.0%, 97.5%)	0 (0.0%, 52.2%)
No brain RT or brain RT >2 months	n=10	n=22
	7 (70.0%) (34.8%, 93.3%)	8 (36.4%) (17.2%, 59.3%)
Intracranial DoR[c]		
No. patients with event/no. of responders (%)		
median, months (95% CI)[d]		
Total	10/14 (71.4%)	11/17 (64.7%)
	12.9 (5.3, 16.5)	12.9 (5.6, 22.1)
Brain radiation status and timing relative to study entry		
No brain RT	5/7 (71.4%)	5/8 (62.5%)
	11.1 (3.7, 12.9)	11.1 (3.7, NE)
≤2 months	5/7 (71.4%)	6/9 (66.7%)
	14.7 (5.3, 22.1)	14.7 (5.3, 22.1)
>2 months	0	0
	N/A	N/A
No brain RT or brain RT >2 months	5/7	5/8 (62.5%)
	11.1 (3.7, 12.9)	11.1 (3.7, NE)

N/A, not applicable; RT, radiation therapy.
[a] by RECIST v1.1.
[b] calculated using Clopper-Pearson method.
[c] Kaplan-Meier estimate.
[d] Computed using method of Brookmeyer and Crowley.

Ancillary analyses

Subgroup analyses

Table 40: Objective Response Rate by Subgroups (BICR Assessment) (CCOD 31 May 2018)

Objective Response Rate (BICR Assessment) by Subgroups, ROS1 NSCLC Efficacy Evaluable enrolled up to APR 30, 2017
Protocols: GO40782, GO40783, GO40784
CCOD: May 31 2018, DBL: Jul 31 2018

			Total (N=53)		
			Patients	Response	
Name	Level	Response	n	n (%)	95% CI for Rate (Clopper-Pearson)
Entrectinib Dose	Below RP2D	Responder	2	2 (100.0%)	(15.81, 100.00)
	At RP2D	Responder	47	37 (78.7%)	(64.34, 89.30)
	Above RP2D	Responder	4	2 (50.0%)	(6.76, 93.24)
ECOG Performance Status	0	Responder	20	19 (95.0%)	(75.13, 99.87)
	1	Responder	27	19 (70.4%)	(49.82, 86.25)
	2	Responder	6	3 (50.0%)	(11.81, 88.19)
Any prior systemic therapy	N	Responder	7	7 (100.0%)	(59.04, 100.00)
	Y	Responder	46	34 (73.9%)	(58.87, 85.73)
Prior chemotherapy	N	Responder	11	10 (90.9%)	(58.72, 99.77)
	Y	Responder	42	31 (73.8%)	(57.96, 86.14)
Prior targeted therapy	N	Responder	44	33 (75.0%)	(59.66, 86.81)
	Y	Responder	9	8 (88.9%)	(51.75, 99.72)
Prior hormonal therapy	N	Responder	52	40 (76.9%)	(63.16, 87.47)
	Y	Responder	1	1 (100.0%)	(2.50, 100.00)
Number of prior systemic therapies	0	Responder	17	15 (88.2%)	(63.56, 98.54)
	1	Responder	23	14 (60.9%)	(38.54, 80.29)
	2	Responder	5	5 (100.0%)	(47.82, 100.00)
	3	Responder	3	3 (100.0%)	(29.24, 100.00)
	4	Responder	3	2 (66.7%)	(9.43, 99.16)
	>4	Responder	2	2 (100.0%)	(15.81, 100.00)
Number of prior anticancer radiation therapies	0	Responder	29	24 (82.8%)	(64.23, 94.15)
	1	Responder	16	11 (68.8%)	(41.34, 88.98)
	2	Responder	2	2 (100.0%)	(15.81, 100.00)
	3	Responder	5	3 (60.0%)	(14.66, 94.73)
	>4	Responder	1	1 (100.0%)	(2.50, 100.00)

ORR by age was 78.6% (33/42) in patients aged ≥18 to <65 years, and 72.7% (8/11) in patients aged ≥65 years. ORR by region was 73.7% (14/19) in EU, 80% (12/15) in USA, and 78.9% (15/19) in all other countries. ORR by prior immunotherapy was 77.1% (37/48) in patients with no prior immunotherapy, and 80% (4/5) in patients with prior immunotherapy.

Table 41: Objective Response Rate by ROS-1 gene fusion partner (BICR Assessment) (CCOD 31 May 2018)

Objective Response Rate (BICR Assessment) by Subgroups, ROS1 NSCLC Efficacy Evaluable enrolled up to APR 30, 2017
Protocols: GO40782, GO40783, GO40784
CCOD: May 31 2018, DBL: Jul 31 2018

			Total (N=53)		
			Patients	Response	
Name	Level	Response	n	n (%)	95% CI for Rate (Clopper-Pearson)
Gene Fusion Partner at Time Enrollment	CD74 - ROS1	Responder	21	18 (85.7%)	(63.66, 96.95)
		CR	21	0 (0.0%)	(0.00, 16.11)
		PR	21	18 (85.7%)	(63.66, 96.95)
		SD	21	0 (0.0%)	(0.00, 16.11)
		PD	21	1 (4.8%)	(0.12, 23.82)
	EZR - ROS1	Responder	5	4 (80.0%)	(28.36, 99.49)
		CR	5	0 (0.0%)	(0.00, 52.18)
		PR	5	4 (80.0%)	(28.36, 99.49)
		SD	5	0 (0.0%)	(0.00, 52.18)
		PD	5	1 (20.0%)	(0.51, 71.64)
	SDC4 - ROS1	Responder	6	4 (66.7%)	(22.28, 95.67)
		CR	6	0 (0.0%)	(0.00, 45.93)
		PR	6	4 (66.7%)	(22.28, 95.67)
		SD	6	0 (0.0%)	(0.00, 45.93)
		PD	6	2 (33.3%)	(4.33, 77.72)
	SLC34A2 - ROS1	Responder	7	4 (57.1%)	(18.41, 90.10)
		CR	7	1 (14.3%)	(0.36, 57.87)
		PR	7	3 (42.9%)	(9.90, 81.59)
		SD	7	0 (0.0%)	(0.00, 40.96)
		PD	7	0 (0.0%)	(0.00, 40.96)
	TPM3 - ROS1	Responder	2	1 (50.0%)	(1.26, 98.74)
		CR	2	0 (0.0%)	(0.00, 84.19)
		PR	2	1 (50.0%)	(1.26, 98.74)
		SD	2	0 (0.0%)	(0.00, 84.19)
		PD	2	0 (0.0%)	(0.00, 84.19)
	Unknown	Responder	12	10 (83.3%)	(51.59, 97.91)
		CR	12	2 (16.7%)	(2.09, 48.41)
		PR	12	8 (66.7%)	(34.89, 90.08)
		SD	12	1 (8.3%)	(0.21, 38.48)
		PD	12	0 (0.0%)	(0.00, 26.46)

APAC: HKG/JPN/KOR/SGP/TWN; EU: AUS/BEL/DEU/ESP/FRA/GBR/ITA/POL/NLD; NA: USA;

Analysis by investigator assessment

ORR by Inv: 75.5% (95% CI: 61.7%, 86.2%). Six patients (11.3%) achieved CR and 34 patients (64.2%) achieved PR.

Concordance in ORR between investigator and BICR was 86.9% (46/53 patients identified as responders/non responders in both assessment). In 3 subjects (5.7%) PD was declared by investigator earlier than BICR, while in 5 cases (9.4%) later than BICR.

DOR by Inv: median DOR for the 40 responders based on the investigator assessment was 16.6 months (95% CI: 13.1, 21.4).

PFS by Inv: median PFS by inv was 15.5 months (95%CI 10.0, 19.0)

Patients excluded from the efficacy evaluable analysis dataset

Subjects excluded from the patients with ROS1-positive NSCLC efficacy evaluable set were the following:

- non-measurable disease (12 months of FU minimum n=3; less than 12 months of FU n=6)

- ECOG PS>2 (n=3)

- ROS1 biomarker ineligible (n=1)

- received prior ROS1 inhibitor (n=27)

Patients who received prior ROS1 inhibitors:

Of a total 27 subjects who received entrectinib after other ROS1 inhibitor, 3 only responded (3/27=11.1%). These 27 ROS1 positive NSCLC patients previously treated with crizotinib (9 in STARTRK-1 and 18 in STARTRK-2) included 19 patients who previously experienced CNS-only progression and 8 overall systemic progression while on crizotinib. A total of 2 responses were

observed among the 19 patients with CNS-progression only (RR 10.5%), and 1 response among 8 patients with overall systemic progression (RR 12.5%).

Patients Reported Outcomes (PROs)

PROs were only evaluated in STARTRK-2 study (i.e. 37 subjects of the 53 included in the ROS1 NSCLC efficacy analysis set). Overall, all patients completed the QLQ-C30 and the QLQ-LC13 questionnaire on Cycle 1 Day 1 and answered at least 1 question on an onstudy time point thereafter. The number of patients with evaluable QLQ-C30 and QLQ-LC13 questionnaires at baseline were 34 (91.9%) and 33 (89.2%) respectively. The completion rates for both questionnaires remained ≥80% at most study visit, but was 42% at the EOT visit. At baseline, patients reported moderate-to-high functioning scores for QLQ-C30 (global health status [57.84], physical functioning [68.87], role functioning [60.29], and cognitive functioning [81.86]). While receiving entrectinib, patients tended to maintain or improve on high baseline health-related quality of life (mean changes ranging from -37.50 to 11.74 on the global health status). For functional scales (e.g., physical functioning, role functioning, and cognitive functioning), patients continued to report moderate-to-high scores at most study visits with a trend towards clinical improvement, with the exception of cognitive functioning which trended towards some worsening at specific timepoints that were above the clinical meaningful threshold of 10-points (worst mean change score of -41.76 at Cycle 22 Day 1). According to the QLQ-LC13, patients reported moderate symptom burden at baseline (chest pain [mean score=17.17], dyspnea [mean score=38.05]), with trends towards immediate improvement. Severe cough was reported at baseline (mean score of 44.44), followed by immediate meaningful improvement (mean change from baseline score of -17.86 on Cycle 2 Day 1).

Molecular analyses

Table 42: Summary of Enrollment by Assay

Efficacy Evaluable Analysis Set	No. of patients	Enrollment assay		
		Pharos	F1/F1H	Others
ROS1	53	25	5	23

F1/F1H =FoundationOne (F1)/FoundationOne Heme (F1H)
Others= other local test (>35 enrollment assays in total; most tests contributed 1-2 patients each)

Concomitant genetic alteration

Only 9 subjects out of 53 ROS1 fusion positive NSCLC patients have additional molecular information.

Secondary resistance

ctDNA in plasma samples collected at baseline and at progression was analysed on NGS FoundationOne Liquid (~70 gene) assay. To date, of the 53 NSCLC ROS1 fusion positive MAA patients, 18 had matched pre and end of treatment plasma collections. 4 patients showed the emergence of the crizotinib resistance mutation (G2032R) at the end of treatment sample, and 1 patient showed the emergence of the ROS1 mutation F2004C at end of treatment collection, which were not present in the pre-treatment samples.

Summary of main efficacy results (integrated ROS1 NSCLC analysis)

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 43 : **Summary of efficacy for ROS1-positive NSCLC pooled analysis**

ROS1 NSCLC Integrated analysis (evaluation of efficacy and safety of oral entrectinib in ROS1-positive adult patients with locally advanced or metastatic NSCLC)			
Study identifier	Integrated analysis of the ROS1-positive NSCLC patients treated within 3 studies: - RXDX-101-02 (STARTRK-2) - ALKA-372-001 (ALKA) - RXDX-101-01 (STARTRK-1)		
Design	Pooled analysis. All patients received entrectinib. The design of the 3 studies were: - STARTRK-2: phase 2 global single arm open label multicenter basket study of oral entrectinib at the RP2D in patients with solid tumor with NTRK, ROS1 or ALK gene fusions. - ALKA and STARTRK-1: phase 1 single arm open label studies of oral entrectinib in patients with solid tumor with NTRK, ROS1 or ALK molecular alterations.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable not applicable not applicable
Hypothesis	Assuming the true ORR by BICR (ORR-BICR) is 70%, a sample size of at least 50 patients yield a 95% 2-sided confidence interval (CI) with precision ±17% that exclude a lower limit of 50%.		
Treatments groups	Entrectinib		Entrectinib orally at or above the RP2D of 600 mg once daily
Endpoints and definitions	Primary endpoints	Objective response rate (ORR)	Proportion of patients with confirmed CR or PR (responders) per RECIST 1.1 by BICR (a confirmed response was a response that persisted on repeat-imaging ≥4 weeks after initial documentation of response)
		Duration of response (DOR)	Time from the date of first objective response (either CR or PR, based on RECIST 1.1 by BICR) to first documentation of radiographic disease progression or the date of death due to any cause, whichever was earlier.
	Secondary endpoints	Time to CNS Progression	Time from first dose of entrectinib to first documentation of radiographic CNS disease progression (i.e. new CNS lesion or progression in any CNS lesion per RECIST 1.1 by BICR) or death due to any cause.
		Progression-Free Survival (PFS)	Time from first dose of entrectinib to first documentation of radiographic disease progression per RECIST v1.1 by BICR or death due to any cause.
		Overall Survival (OS)	Time from the first dose of entrectinib to the date of death due to any cause.
	Intracranial specific endpoints (evaluated in the subpopulation with CNS disease at baseline)	Intracranial Objective Response Rate (IC-ORR)	Proportion of patients with confirmed CR or PR in the CNS lesion(s) per RECIST 1.1 by BICR (intracranial responders). Confirmed response persisted on repeat-imaging ≥4 weeks after initial documentation of response.
		Intracranial-Duration of Response (IC-DOR)	Time from the date of first intracranial response to first documentation of radiographic CNS disease progression (per RECIST 1.1 by BICR) or date of death due to any cause, whichever was earlier.
		Intracranial Progression-Free Survival (IC-PFS)	Time from first dose of entrectinib to first documentation of radiographic CNS disease progression (i.e. new CNS lesion or progression in any CNS lesion per RECIST 1.1 by BICR) or death due to any cause.
Database lock	Patients enrolled up to 30 April 2017 Updated Clinical cut off date (CCOD) 1 May 2019		
Results and Analysis			
Analysis description	**Updated Analysis (primary analysis included n=53 patients)**		

Analysis population and time point description	Other: ROS1 NSCLC efficacy population (pooled from 3 studies) Patients must met all the following criteria: - ROS1-positive status with no co-occurrence with other oncogenic drivers - Advanced or metastatic NSCLC - measurable disease at baseline as assessed by investigator - Received at least 1 dose of entrectinib - Not treated previously with a ROS1 inhibitor (e.g. crizotinib) - Had ≥12 months follow up after first response	
Descriptive statistics	Treatment group	entrectinib
	Number of subject	**94**
	ORR rate (95%CI)	**73.4%** **(63.3, 82.0)**
	DOR Patients with event (%) median (months) (95%CI)	**16.5** **(14.6, 28.6)**
	Time to CNS progression Patients with event (%) Median (months) (95%CI)	**24.8** **(16.1, NE)**
	PFS Patients with event (%) median (months) (95%CI)	**16.8** **(12.0, 21.4)**
	OS Patients with event (%) median (months) (95%CI)	**NE** **(28.3, NE)**
	Number of subject with CNS disease at baseline by BICR	**34**
	IC-ORR rate (95%CI)	**50%** **(32.4, 67.6)**
	IC-DOR Patients with event (%) median (months) (95%CI)	**12.9** **(5.6, 22.1)**
Notes	A larger dataset wich include n=161 subjects has been provided per CHMP request. Those subjects have >6 months fu (vs >12 months FU per iSAP). Median survival follow up is 15.8 months (95%CI 14.49, 18.23). ORR 67.1% (responders 108/161) (95%CI 59.25, 74.27) DOR median 15.7 months (95%CI 13.9, 28.6); patients with DOR event 44.4% (48/108) PFS median 15.7 months (95%CI 11.0, 21.1); patients with PFS event 50.9% (82/161) OS median NE (95%CI 28.3, NE); patients with OS event 23.6% (38/161) Of those 161 subjects, 46 had CNS disease at baseline. IC-ORR was 52.2% (24/46) (95%CI 36.95, 67.1), which includes 8 CR (17.4%). Of those, 24 had measurable CNS disease by BIRC, in whom IC-ORR was 79.2% (19 responders) (95%CI 57.85, 92.9); IC-DOR in the 19 responders was 12.9 months (95%CI 6.8, 22.1).	

Clinical studies in special populations

Table 44: Elderly Patients (≥65 Years) in the ROS1 NSCLC Efficacy Evaluable Population (N=161)

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	0	0	0
Non Controlled trials			
ALKA	2/9	0/9	0/9
STARTRK-1	1/7	0/7	0/7
STARTRK-2	29/145	6/145	1/145

Supportive study(ies)

WO40977 Non-Interventional Study (for the ROS1 NSCLC indication)

In order to bring additional evidence in support of the ROS1 NSCLC application for entrectinib, and to compensate the lack of a direct comparative data from a randomized clinical trial, the Applicant submitted a retrospective non-interventional study, real world comparative analysis of the integrated clinical data (STARTRK-2, STARTRK-1, and ALKA studies) of ROS1-positive NSCLC patients treated with entrectinib versus real world matched patients treated with crizotinib. Crizotinib (XALKORI) is currently the only ROS1 inhibitor approved in the EU and USA for the treatment of adults with ROS1-positive NSCLC. The source of the real world data (RWD) for crizotinib was the Flatiron Health Analytic Database (New York, NY, USA).

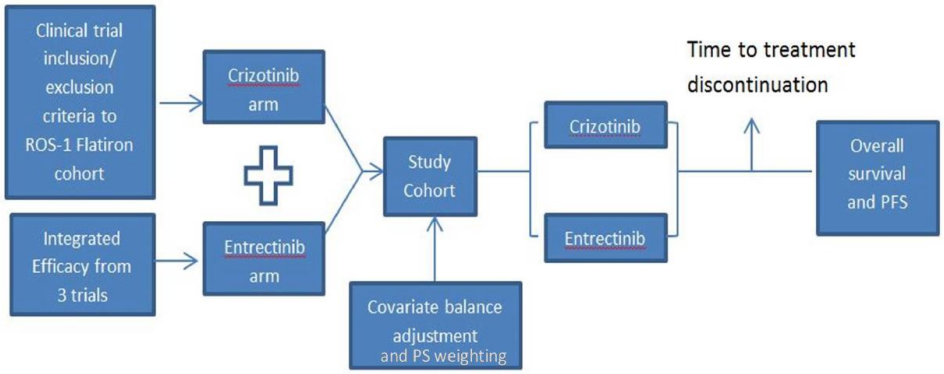


Figure 14: Study schema showinmg the overall study design

Time to treatment discontinuation (TTD) was used as primary endpoint, defined as:

- TTD: For the entrectinib arm, TTD was defined as date from the initiation of entrectinib to treatment discontinuation.
- In the crizotinib arm, TTD was defined as the date of the initiation of crizotinib to treatment discontinuation.

Secondary objectives of the study included PFS and OS, as well as description of demographics, clinical characteristics and outcomes of the ROS1-positive NSCLC patients with and without CNS metastases at baseline (including time to CNS progression).

The entrectinib arm was the ROS1 NSCLC Efficacy Evaluable analysis set obtained by integrating data from STARTRK-2, STARTRK-1, and ALKA studies (n=53). For crizotinib, all patients from the Flatiron

database retained after application of inclusion and exclusion criteria derived from the STARTRK-2 pivotal study (used also for the integrated efficacy analysis set of entrectinib) were considered (n=69), from whom a matched crizotinib arm (n=54) was derived for the comparative analysis.

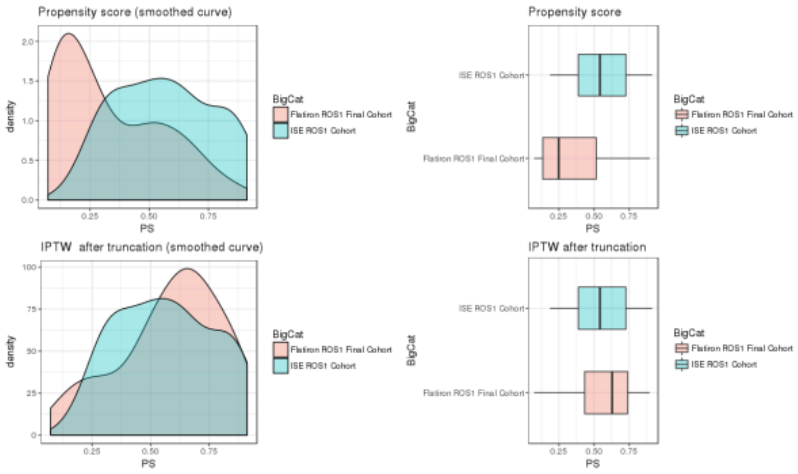
Table 45: Patient populations at baseline

	Entrectinib Arm	Crizotinib Arm
Baseline Demographics	Patients with locally advanced or metastatic NSCLC, ≥ 18 years of age	Patients with locally advanced or metastatic NSCLC, ≥ 18 years of age
Performance Status	ECOG performance status of 0–2	ECOG performance status of 0–2; Patients with missing ECOG were allowed
Testing	ROS1–positive rearrangement confirmed via NGS or other nucleic acid based diagnostic tests	ROS1–positive rearrangement confirmed, confirmed via NGS, FISH or IHC, as per U.S. clinical practice
Prior Therapies	Prior anticancer therapy such as chemotherapy allowed, and no previous exposure to another ROS1 inhibitor such as crizotinib*	Prior anticancer therapy such as chemotherapy allowed; Patients who had a gap between advanced diagnosis date and a crizotinib first treatment start date of more than 90 days AND no information on treatment prior crizotinib start were excluded.

ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; NGS = next-generation sequencing; NSCLC = non-small cell lung cancer; U.S. = United States.

*Two patients previously reporting to have been treated with crizotinib for a short period due to intolerance were enrolled in the trial and included in this analysis.

Matched propensity score distribution were obtained with the matched crizotinib arm (n=54):



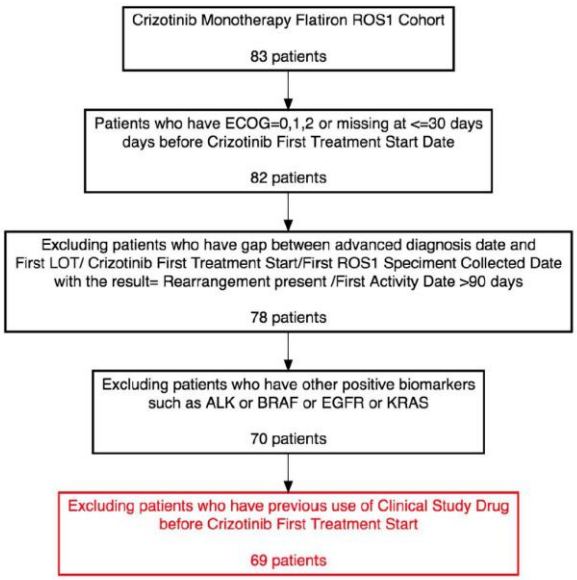
IPTW = inverse probability of treatment weighting; ISE = integrated summary of efficacy; PS = propensity score

Table 12 shows SMD were computed for all continuous and categorical covariates in the unadjusted sample (no PS) and adjusted sample.

Figure 15: Propensity score distribution on all population (Top) and after weighting and truncation (Bottom)

Descriptive statistics, evaluation of prognostic factors to be used for the development of a propensity score, definition of a matched crizotinib population (matched crizotinib arm), and comparison with the entrectinib arm were planned.

A cohort of 150 ROS1 positive advanced (on or after 1/1/2011) NSCLC patients was received by Flatiron. Of those, a total of 63 were in the end selected.



ECOG = Eastern Cooperative Oncology Group, LOT = lines of therapy

Figure 16: Final attrition arm of the real world crizotinib arm

Primary endpoint: TTD

Table 46: Median TTD in entrectinib and crizotinib arms (unweighted and weighted)

Treatment arm	Patients	Events	Median TTD	95% CI
Entrectinib	53	36	14.61	8.29-23.75
Crizotinib Unweighted	69	50	8.36	6.18-10.13
Crizotinib Weighted*	54	42	8.82	8.22-9.9

TTD = time to treatment discontinuation

*N on reweighted sample

Progression events via BICR and investigator in the entrectinib arm

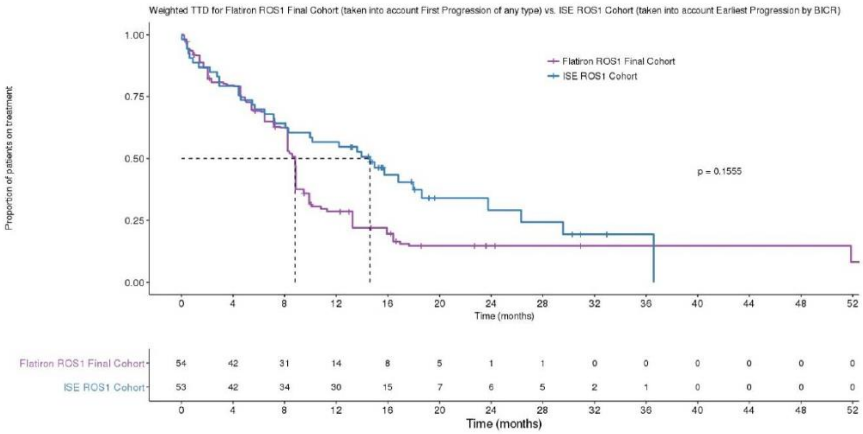
Table 47: Multivariate COX model of entrectinib on TTD in unadjusted, co-variate adjusted and re-weighted samples

Model	Entrectinib vs crizotinib HR (95% CI)
Unadjusted	0.697 (0.451-1.077)
Covariate adjusted*	0.655 (0.399-1.075)
PS weighted	0.637 (0.4-1.015)

HR = hazard ratio; TTD = time to treatment discontinuation

*age, race, gender, smoking status, presence of brain metastases and exposure to prior lines of therapy

Progression events via BICR or investigator in the entrectinib arm



BICR = blinded independent central review; ISE = integrated summary of efficacy; TTD = time to treatment discontinuation

Figure 17: Kaplan Meier estimates of weighted TTD across the arms (BICR)

Secondary endpoint: PFS

Table 48: Median PFS in entrectinib and crizotinib arms (unweighted and weighted)

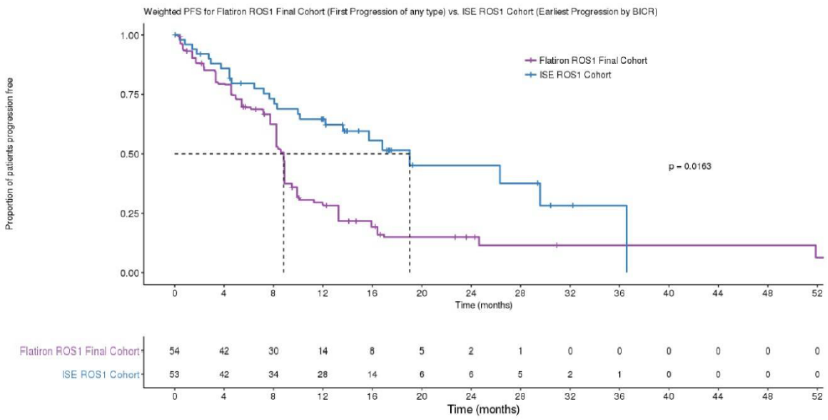
Treatment arm	Patients	Events	Median PFS (95% CI)
Entrectinib	53	25	19.0 (12.2-NE)
Crizotinib Unweighted	69	50	8.49 (6.18-10.13)
Crizotinib Weighted*	54	42	8.82 (8.22-9.9)

NE = not estimated; PFS = progression-free survival
Progression events by BICR in the entrectinib arm
*n represents the reweighted sample

Table 49: Multivariate COX model of treatment effect of entrectinib on PFS in unadjusted, co-variate adjusted and re-weighted samples

Model	Entrectinib vs crizotinib HR (95% CI)
Unadjusted	0.493 (0.303-0.801)
Covariate adjusted*	0.425 (0.245-0.738)
PS IPWT	0.439 (0.26-0.742)

Trial assessment of progression is BICR
PS: propensity score; IPWT: Inverse probability of treatment weight
Progression events are BICR in the entrectinib arm
*age, race, gender, smoking status, presence of brain metastases and exposure to prior lines of therapy



BICR = blinded independent central review; ISE = integrated summary of efficacy; PFS = progression-free survival

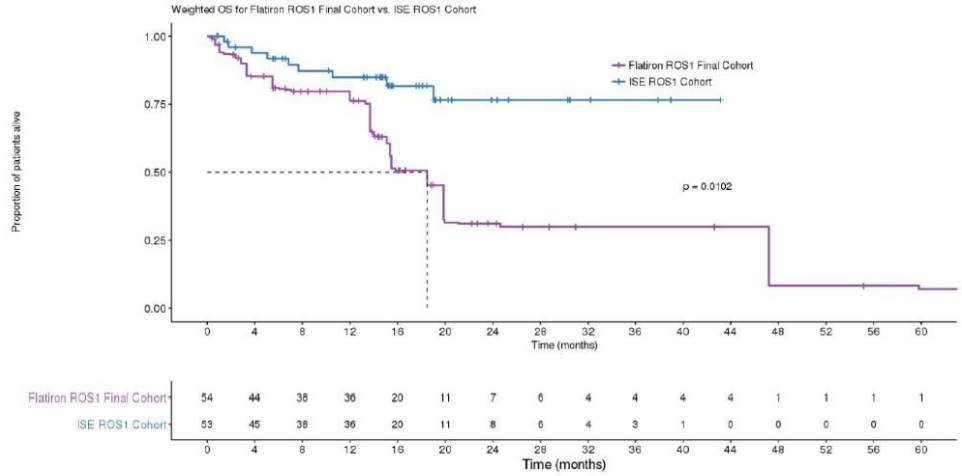
Figure 18: Kaplan Meier estimates of weighted PFS across the arms (progression confirmed by BICR in entrectinib arm)

Secondary endpoint: OS

Table 50: Median OS in entrectinib and crizotinib arms (unweighted and weighted)

Treatment arm	Patients*	Events	Median OS (95% CI)
Entrectinib	53	9	NE
Crizotinib Unweighted	69	33	19.87 (15.1-NE)
Crizotinib Weighted*	54	34	18.49 (15.1-19.93)

OS = overall survival; NE = not estimated
*N based on weighted sample



ISE = integrated summary of efficacy; OS = overall survival

Figure 19: Kaplan Meier estimates of OS (weighted OS for the crizotinib arm)

Subgroup analysis on CNS metastases: Among the 69 ROS1 positive patients from Flatiron US database who received crizotinib in the real word, the Applicant identified 17 subjects with brain metastasis. Several differences in baseline characteristics of patients with CNS disease at baseline receiving entrectinib in clinical trials and crizotinib in the real world were observed (data not shown). Estimated median PFS was 4.6 months and median OS was 15.5 months in the CNS disease subgroup treated with crizotinib. No data on intracranial response to crizotinib are available.

2.5.4. NTRK gene fusion positive solid tumours indication

Integrated analysis of efficacy for NTRK gene fusion positive solid tumours

An integrated efficacy analysis has been presented to support the sought indication of entrectinib for the treatment of adult and paediatric patients with NTRK fusion-positive solid tumour, who have progressed following prior therapies or as initial therapy when there are no acceptable standard therapies. This was conducted based on the NTRK Efficacy Evaluable Analysis Set, composed of 54 adult patients with NTRK fusion-positive solid tumour treated with at least one dose of entrectinib across the three studies in adult patients with solid tumours (ALKA, STARTRK-1, and STARTRK-2). All patients included in the NTRK Efficacy Evaluable Analysis Set had measurable disease at baseline and at least 6 months follow-up. Patients included were enrolled up to 30 November 2017.

During the procedure, as per CHMP request, data on additional patients and updated analyses have been provided (see table below). The latest dataset include 74 adult patients with >6 months of FU.

Primary CNS tumors, and paediatric patients, have been analysed and reported separately.

Table 51: Available Analyses of Efficacy and Safety of Entrectinib in Integrated NTRK Efficacy Evaluable and Safety Populations

Analysis dataset	Cutoff dates		No. of patients in analysis set		Comments
	ECOD	CCOD	Efficacy	Safety	
MAA	30 Nov 2017	31 May 2018	n=54	n=355	**Efficacy**: Pooled adult patients from ALKA, STARTRK-1 and STARTRK-2. All patients had ≥6 months of efficacy follow-up at time of CCOD. Separate efficacy data was provided for 6 adult patients with primary brain tumors, and 1 paediatric patient. All information was presented in NTRK SCE (2.7.3). **Safety:** Pooled patients from ALKA, STARTRK 1, STARTRK 2 and STARTRK-NG (paediatric). All information was presented in NTRK SCS (2.7.4).
At the time of D120	30 Nov 2017	31 Oct 2018	n=54	n=355	**Efficacy:** Pooled adult patients from ALKA, STARTRK-1 and STARTRK-2. Separate efficacy data was provided for 6 adult patients with primary brain tumors, and 1 paediatric patient. All patients had ≥ 11 months of efficacy follow-up at time of CCOD. All information was presented in NTRK Supplementary Efficacy report in eCTD Module 5, and a summary of adult data in D120 response to questions 74 and 159. **Safety:** Pooled patients from ALKA, STARTRK 1, STARTRK 2 and STARTRK-NG (paediatric). All information was presented in NTRK Supplementary Safety report in eCTD Module 5, and in the responses to D120 safety questions. The EU Product Information and EU-RMP have been updated as well based on this updated information.
At the time of D120 and D180	31 Oct 2018	31 Oct 2018	n=92*; >6 mo FU (n=74*) <6 mo FU (n=18)	504	**Efficacy:** Pooled adult patients from ALKA, STARTRK-1 and STARTRK-2. This included 38 additional patients compared to the MAA dataset (enrolled into ALKA, STARTRK-1 or STARTRK-2 between 30 Nov 2017 and 31 Oct 2018). Analysis of primary efficacy endpoints (ORR, BOR and DoR all by BICR) presented by tumor type and follow-up duration were included in D120 response to question 74, and response to D180 question 27. In addition, data on 8 adult patients with primary brain tumours was provided in response to D120 question 159, and 5 paediatric patients in response to D120 questions 77, 114 and 159. At time of D180 the EU Product Information and EU-RMP were updated based on this recent information for N=74. **Safety:** Pooled patients from ALKA, STARTRK 1, STARTRK 2 and STARTRK NG. Full updated safety information is included in new D180 safety supplementary report in Module 5. The EU Product Information and EU-RMP are updated as well based on this information.

ECOD=Enrolment cutoff date, CCOD=clinical cutoff date; MAA=marketing authorization application. FU=Follow-up.

* At D120 responses, data regarding a total of 93 subjects (75 with >6 months FU) were provided. However, the Applicant has subsequently discovered that one patient initially diagnosed with breast cancer harbouring a MYO5A-NTRK3 by local laboratory assessment, was shown to have a coexisting ALK fusion by Pharos central testing. This patient has therefore been excluded from the efficacy evaluable population due to the presence of a coexisting oncodriver, and all subsequently analyses include 74 adult patients with >6 months FU.

Methods

Study participants

For the efficacy analysis, data were pooled across the 3 clinical studies ALKA, STARTRK-1 and STARTRK-2 in adults (age ≥18 years). Patients must meet all of the following criteria to be included in the NTRK efficacy population:

- Have tumours that harbor an NTRK gene fusion

- Received at least 1 dose of entrectinib
- Has an extracranial solid tumor (i.e. exclusion of primary brain tumor)
- Not treated previously with a TRK inhibitor

Molecular characterisation of tumor tissue: *see ROS1 NSCLC integrated efficacy analysis.*

Treatments

At least one dose of entrectinib at (n=51) or above (n=3) the RP2D of 600 mg.

Objectives/Outcomes/endpoints

See ROS1 NSCLC integrated efficacy analysis.

Sample size

By assuming the true ORR by BICR was 60%, a sample size of 56 patients yield a 95% 2-sided CI with precision ±14% that exclude a lower limit of 30%.

Statistical methods

The integrated efficacy analyses were based on NTRK efficacy evaluable analysis set.

Summary statistics with 95% 2-sided CIs properly calculated were used.

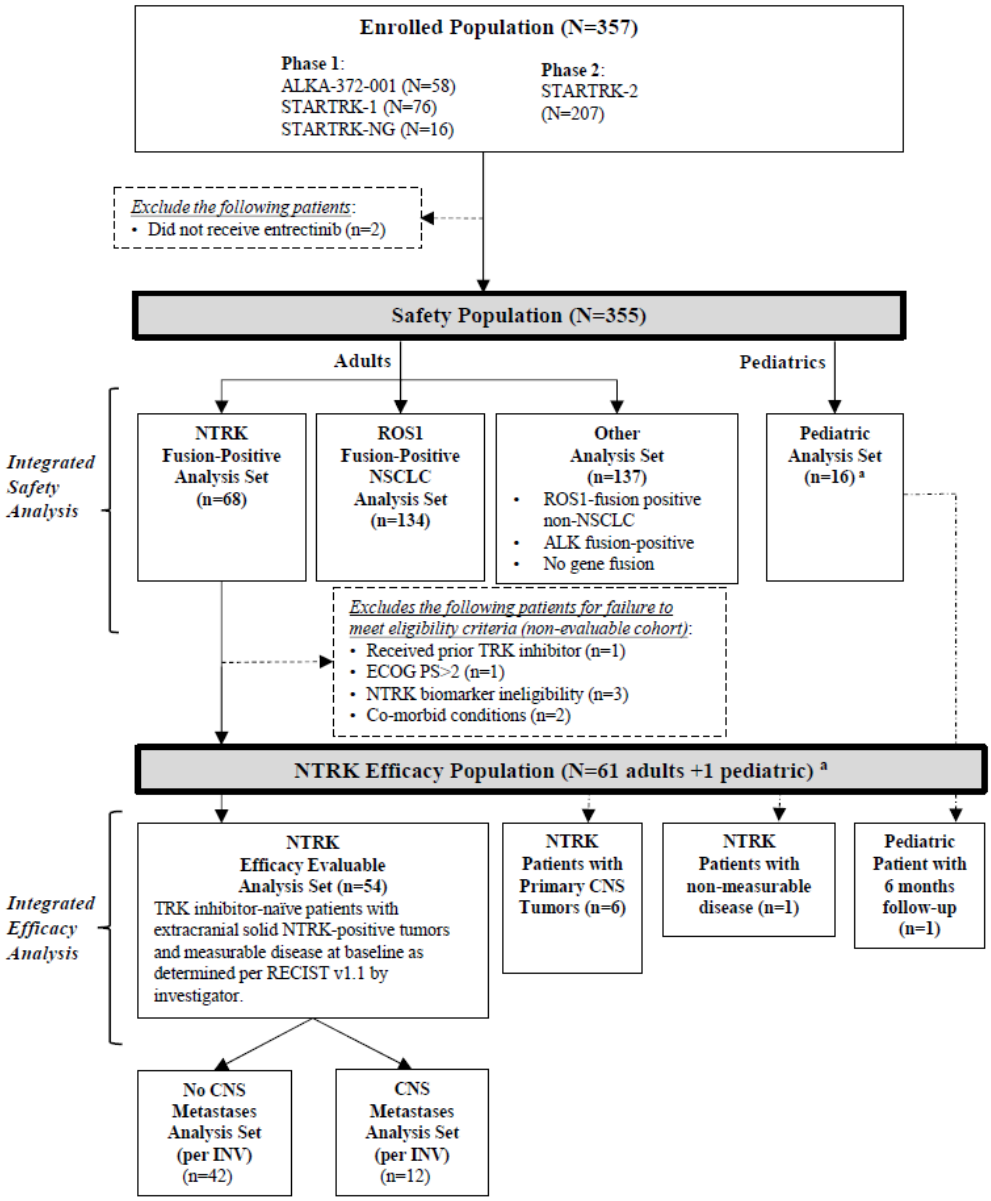
ORR, CBR, IC-ORR: proportion and corresponding 2-sided 95% Clopper-Pearson exact CI.

time-to-event endpoints (DOR, PFS, OS, IC-DOR, IC-PFS, Time to CNS progression): median, 25th, and 75th percentiles estimated by using the Kaplan-Meier method. The associated 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowly (1982) and Klein and Moeschberger (1997). Landmark analyses at 6, 9, and 12 months were provided with the corresponding 2-sided 95% CIs calculated using the method of Kalbfleisch and Prentice (1980). Kaplan-Meier curves will be presented.

waterfall and swimmer plots were used to depict each patient's best tumor response (BOR) and time on study, respectively, including time to first objective response by BICR (if applicable) and DOR.

Formal significance tests were not performed. No statistical adjustment was made to address the sources of multiplicity associated with the integrated analysis. Statistical analyses were carried out overall, by study, by CNS-disease status at baseline. Sensitivity analyses were carried out to assess robustness of findings. Exploratory /sensitivity analyses in the NTRK efficacy nonevaluable analysis set were planned. Data from patients with primary CNS tumors were presented separately. Conduction of interim analysis for Breakthrough Therapy Designation Submission (27 January 2017, n=19 NTRK fusion-positive patients; an integrated BTD SAP version 1.0, 14 November 2016), and interim analysis for marketing application submission were considered.

SAP revisions: *See ROS1 NSCLC integrated efficacy analysis.* **Results**



ALK=anaplastic lymphoma kinase; CNS=central nervous system; ECOG PS=Eastern Cooperative Oncology Group performance status; INV=investigator; NSCLC=non-small cell lung cancer; NTRK=neurotrophic tyrosine receptor kinase; RECIST=Response Evaluation Criteria for Solid Tumors; TRK=tropomyosin receptor kinase.

[a] In addition, 4 pediatric patients with tumors harboring an NTRK gene fusion have been enrolled after 30 November 2017 in the expansion portion of STARTRK-NG. Preliminary efficacy data (<6 months follow-up) for these 4 pediatric patients are provided in Appendix 2. Additional efficacy follow-up (at least 6 months) is planned to be submitted at the time of safety follow-up.

Figure 20: Patient populations and analyses sets for patients with NTRK gene fusion positive solid tumours supporting the indication

Baseline data

Table 52: Key Demographic and Baseline Disease Characteristics of Adult NTRK Efficacy Evaluable Patients Enrolled up to 30 April 2018

			MAA primary NTRK efficacy evaluable	D120 NTRK efficacy evaluable
	Enrolment cutoff date		30 Nov 2017	30 April 2018
			N=54	**N=74**
Demographics	Age	median (range), years	57.5 (21-83)	57.0 (21-83)
		≥65 years, n (%)	20 (37.0)	26 (35.1)
	Sex, n (%)	male	22 (40.7)	35 (47.3)
		female	32 (59.3)	39 (52.7)
	Race, n (%)	White	43 (79.6)	52 (70.3)
		Asian	7 (13.0)	13 (17.6)
		Black or African American	0	2 (2.7)
		not reported	4 (7.4)	7 (9.5)
	ECOG PS, n (%)	0	23 (42.6)	30 (40.5)
		1	25 (46.3)	34 (45.9)
		2	6 (11.1)	10 (13.5)
	History of smoking, n (%)		23 (43.4)	29 (40.3)
Baseline Disease Characteristics	Tumor type (High Level), n (%)			
		Breast	6 (11.1)	6 (8.1)
		Cholangiosarcoma	1 (1.9)	1 (1.4)
		CRC	4 (7.4)	7 (9.5)
		GI other	0	1 (1.4)
		Gynecological	2 (3.7)	2 (2.7)
		Neuroblastoma	0	1 (1.4)
		Neuroendocrine	3 (5.6)	4 (5.4)
		NSCLC	10 (18.5)	13 (17.6)
		Pancreatic	3 (5.6)	3 (4.1)
		Salivary (MASC)	7 (13.0)	13 (17.6)
		Sarcoma	13 (24.1)	16 (21.6)
		Thyroid	5 (9.3)	7 (9.5)
	NTRK gene fusion, n (%)	*NTRK1*	22 (40.7)	30 (40.5)
		NTRK2	1 (1.9)	2 (2.7)
		NTRK3	31 (57.4)	42 (56.8)
	median time since diagnosis, months (range)		21.4 (2.1-433.1)	21.0 (2.1-433.1)
	Disease stage at initial diagnosis, n (%)		(n=53)[a]	(n=73)[a]
		0	1 (1.9)	2 (2.7)
		I (A/B)	6 (11.3)	7 (9.6)
		II (A/B)	8 (14.8)	12 (16.4)
		III (A/B/C)	12 (22.6)	15 (20.3)
		IV	21 (39.6)	30 (41.1)
		unknown	5 (9.4)	7 (9.6)
	Metastatic disease	any site, n (%)	52 (96.3)	72 (97.3)
		bone, n (%)	17 (31.5)	20 (27.0)
		brain, n (%)	12 (22.2)	19 (25.7)
		liver, n (%)	21 (38.9)	28 (37.8)
		lung, n (%)	33 (61.1)	45 (60.8)
		lymph nodes, n (%)	30 (55.6)	39 (52.7)
		skin, n (%)	3 (5.6)	4 (5.4)
		other, n (%)	15 (27.8)	25 (33.8)
Previous Cancer Treatment	No of prior systemic therapies[a], n (%)	0	14 (25.9%)[c]	20 (27.0%)
		1	15 (27.8%)	21 (28.4%)
		2	16 (29.6%)	20 (27.0%)
		3	4 (7.4%)	6 (8.1%)
		4	4 (7.4%)	4 (5.4%)
		>4	1 (1.9%)	3 (4.1%)
	Previous therapy, n (%)	any systemic therapy[b]	48 (88.9%)	64 (86.5%)
		surgery	43 (79.6%)	61 (82.4%)
		radiotherapy	36 (66.7%)	47 (63.5%)
	Baseline CNS lesions by INV		n=12	n=19
	Prior radiotherapy to brain, n (%)		8[d] (66.7%)	13 (68.4%)

[a] Lines of therapy are determined from the time of metastatic disease diagnosis. Patients may have received other therapies in the adjuvant or neo-adjuvant setting.

[b] Includes any chemotherapy, immunotherapy, targeted therapy or hormonal therapy.

[c] The previous lines of cancer therapy were erroneously reported (as 0) for six NTRK adult patients in the initial SCE (2.7.3) and have been corrected in this table.

[d] one patient with CNS disease at baseline had received halocraneal radiation therapy <2 months before entrectinib treatment which was incorrectly reported in the analysis presented in the initial SCE.

Table 53: Gene Fusion and tumour classification, NTRK Efficacy Evaluable Analysis Set, enrolled up to NOV 30, 2017, CCOD: May 31 2018

Protocols: GO40782, GO40783, GO40784
Enrollment cutoff: Nov 30 2017, CCOD: May 31 2018, DBL: Jul 31 2018

Gene Fusion Tumor Type (High Level) Tumor Type (Low Level)	ALKA (N=1)	ST01 (N=2)	ST02 (N=51)	Total (N=54)
NTRK1				
BREAST	0	0	2 (3.9%)	2 (3.7%)
BREAST (NON-SECRETORY)	0	0	2 (3.9%)	2 (3.7%)
GI - CRC	1 (100.0%)	0	1 (2.0%)	2 (3.7%)
CRC	1 (100.0%)	0	1 (2.0%)	2 (3.7%)
GI - NON-CRC	0	0	4 (7.8%)	4 (7.4%)
CHOLANGIOCARCINOMA	0	0	1 (2.0%)	1 (1.9%)
PANCREATIC	0	0	3 (5.9%)	3 (5.6%)
HEAD AND NECK	0	0	1 (2.0%)	1 (1.9%)
PAPILLARY THYROID	0	0	1 (2.0%)	1 (1.9%)
SARCOMA	0	0	7 (13.7%)	7 (13.0%)
CERVICAL ADENOSARCOMA	0	0	1 (2.0%)	1 (1.9%)
ENDOMETRIAL STROMAL SARCOMA	0	0	1 (2.0%)	1 (1.9%)
FOLLICULAR DENDRITIC CELL SARCOMA	0	0	1 (2.0%)	1 (1.9%)
SARCOMA (NOS)	0	0	4 (7.8%)	4 (7.4%)
THORACIC	0	1 (50.0%)	5 (9.8%)	6 (11.1%)
NSCLC	0	1 (50.0%)	5 (9.8%)	6 (11.1%)
NTRK2				
NEUROENDOCRINE	0	0	1 (2.0%)	1 (1.9%)
NEUROENDOCRINE	0	0	1 (2.0%)	1 (1.9%)
NTRK3				
BREAST	0	0	4 (7.8%)	4 (7.4%)
BREAST (SECRETORY)	0	0	4 (7.8%)	4 (7.4%)
GI - CRC	0	0	2 (3.9%)	2 (3.7%)
CRC	0	0	2 (3.9%)	2 (3.7%)
GYNECOLOGICAL	0	0	2 (3.9%)	2 (3.7%)
ENDOMETRIOID	0	0	1 (2.0%)	1 (1.9%)
OVARIAN	0	0	1 (2.0%)	1 (1.9%)
HEAD AND NECK	0	1 (50.0%)	10 (19.6%)	11 (20.4%)
MASC	0	1 (50.0%)	6 (11.8%)	7 (13.0%)
PAPILLARY THYROID	0	0	2 (3.9%)	2 (3.7%)
THYROID - OTHER	0	0	2 (3.9%)	2 (3.7%)
NEUROENDOCRINE	0	0	2 (3.9%)	2 (3.7%)
NEUROENDOCRINE	0	0	2 (3.9%)	2 (3.7%)
SARCOMA	0	0	6 (11.8%)	6 (11.1%)
DEDIFFERENTIATED CHONDROSARCOMA	0	0	1 (2.0%)	1 (1.9%)
GIST	0	0	1 (2.0%)	1 (1.9%)
MPNST	0	0	1 (2.0%)	1 (1.9%)
SARCOMA (NOS)	0	0	3 (5.9%)	3 (5.6%)
THORACIC	0	0	4 (7.8%)	4 (7.4%)
NSCLC	0	0	4 (7.8%)	4 (7.4%)

Patient diagnosis and tumor histology are mapped by the sponsor to a high-level and low-level term.

Numbers analysed

Table 54: Patient Disposition for Study, (NTRK Efficacy Evaluable Analysis Set) enrolled up to April 30, 2018, CCOD October 31, 2018.

	ALKA (N=1)	ST01 (N=2)	ST02 (N=71)	Total (N=74)
Study Status				
Ongoing	0	0	43 (60.6%)	43 (58.1%)
Discontinued	1 (100.0%)	2 (100.0%)	28 (39.4%)	31 (41.9%)
Death	0	0	23 (82.1%)	23 (74.3%)
Informed Consent Withdrawn	0	0	5 (17.9%)	5 (16.1%)
Lost To Follow-Up	1 (100.0%)	0	0	1 (3.2%)
Other	0	2 (100.0%)	0	2 (6.5%)

Table 55: Patient Disposition for Entrectinib Treatment (NTRK Efficacy Evaluable Analysis Set) enrolled up to April 30, 2018, CCOD October 31, 2018.

Discontinued Treatment	ALKA (N=1)	ST01 (N=2)	ST02 (N=71)	Total (N=74)

	1 (100.0%)	2 (100.0%)	42 (59.2%)	45 (60.8%)
Adverse Event	0	0	9 (21.4%)	9 (20.0%)
Informed Consent Withdrawn	0	0	2 (4.8%)	2 (4.4%)
Progressive Disease	1 (100.0%)	2 (100.0%)	31 (73.8%)	34 (75.6%)

A total of 31 subjects (39.2%) were still on treatment at the CCOD of October 31, 2018.

Outcomes and estimation

A summary of the results in the datasets presented throughout the procedure is presented below:

Table 56: Overview of Updated Efficacy of Entrectinib in Adult Patients with NTRK Fusion-Positive Solid Tumors as Assessed by BICR and >6 months Follow-Up (NTRK Efficacy-Evaluable Analysis Set)

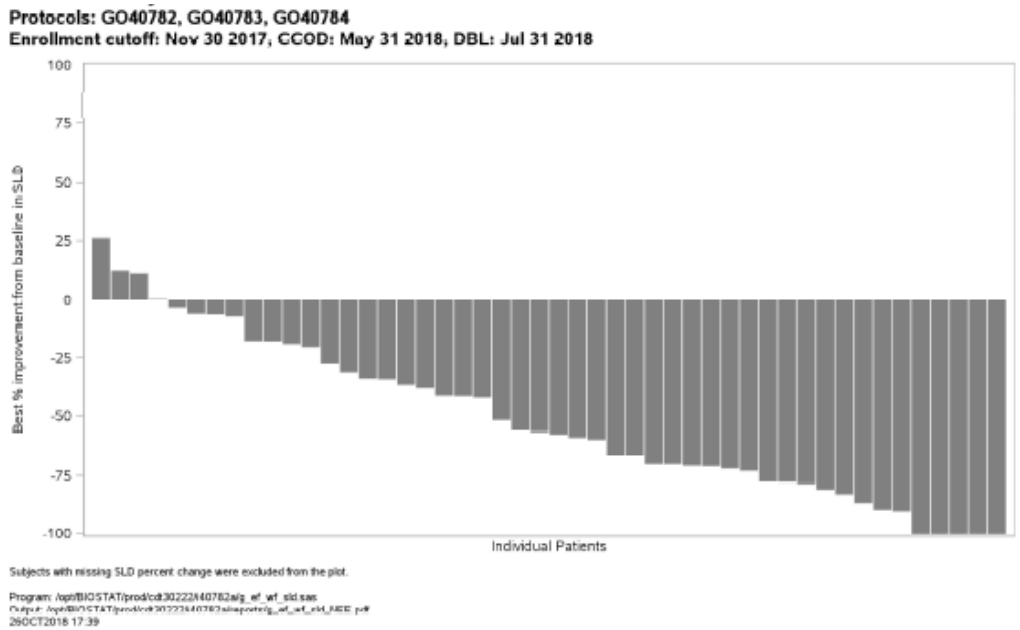
Analysis Dataset	**MAA[a]**	**D120[c]**	
Enrolment cutoff date	30 Nov 2017	30 Nov 2017 to 30 April 2018	30 April 2018
Clinical cutoff date	31 May 2018	31 Oct 2018	31 Oct 2018
Total no. patients enrolled	**N=54**	**N=20**	**N = 54 + 20 = 74**
Median Duration of Survival Follow up. months (range)	12.9 (0.6*-24.7)	7.6 (0.1*-10.4)	14.2 (0.1*-29.7)
Primary Endpoints (BICR-assessed, RECIST v1.1)			
Objective Response Rate (ORR)			
No. of patients with confirmed CR or PR, n	31	15	47
ORR, % (95% CI)[d]	57.4% (43.2, 70.8)	75.0% (50.9, 91,3)	63.5% (51.5, 74.4)
Complete Response, n (%)	4 (7.4%)	1 (5.0%)	5 (6.8%)
Partial Response, n (%)	27 (50.0%)	14 (70.0%)	42 (56.8%)
Stable Disease, n (%)	9 (16.7%)	1 (5.0%)	9 (12.2%)
Progressive Disease, n (%)	4 (7.4%)	2 (10.0%)	6 (8.1%)
non CR/non-PD	3 (5.6%)	0	3 (4.1%)
Missing or unevaluable	7 (13.0%)	2 (10.0%)	9 (12.2%)
Duration of Response (DOR)			
No. of patients with events, n (% of responders)	16/31 (51.6%)	3/15 (20.0%)	21/47 (44.7%)
Median, months (95% CI)[e]	10.4 (7.1, NE)	NE (5.6, NE)	12.9 (9.3, NE)
Event-free probability (95% CI)[e]			
6 months[f]	0.69 (0.51, 0.86)	0.65 (0.31, 0.99)	0.71 (0.58, 0.85)
12 months[f]	0.49 (0.29, 0.70)	NE	0.55 (0.39, 0.72)
Secondary Endpoints (BICR-assessed, RECIST v1.1)			
Clinical Benefit Rate (CBR)			
No of patients with confirmed CR or PR, or SD ≥6 months	35	15	50
CBR, % (95% CI)[d]	64.8% (50.6, 77.3)	75.0% (50.9, 91.3)	67.6% (55.7, 78.0)
Progression-Free Survival			
No. of patients with event, n (%)	29 (53.7%)	8 (40%)	41 (55.4%)
Median, months (95% CI)[e]	11.2 (8.0, 14.9)	NE (6.5, NE)	11.2 (8.0, 15.7)
Time to CNS Progression			
No. of patients with event, n (%)	17 (31.5%)	6 (30.0%)	27 (36.5%)
Median, months (95% CI)[e]	17.0 (14.3, NE)	8.9 (7.6, NE)	16.8 (14.3, NE)
Overall Survival			
No. of patients with event, n (%)	16 (29.6%)	5 (25.0%)	24 (32.4%)
Median, months (95% CI)[e]	20.9 (14.9, NE)	NE (8.9, NE)	23.9 (16.0, NE)

NE, not estimable. n/a, not available at the time of writing.
[a] Full efficacy results presented in Summary of Clinical Efficacy (Module 2.7.3).
[b] Full efficacy results presented in Supplementary Results Report.
[c] patients with ≥6 months of efficacy follow-up at time of CCOD.
[d] Confidence Intervals (CI) calculated using the Clopper-Pearson method.
[e] Median and percentiles for time-to-event analyses based on Kaplan-Meier estimates. Confidence Intervals (CI) for the median were computed using the method of Brookmeyer and Crowley.
[f] Event-Free Probabilities are Kaplan-Meier estimates and confidence intervals were calculated using the method of Kalbfleisch and Prentice.

ORR

Table 57: Objective Response (confirmed) and Best Overall Response, BICR Assessment (NTRK Efficacy Evaluable Analysis Set) CCOD 31 OCT 2018

	ALKA (N=1)	ST01 (N=2)	ST02 (N=51)	Total (N=54)
Responders	0	2 (100.0%)	30 (58.8%)	32 (59.3%)
Non-Responders	1 (100.0%)	0	21 (41.2%)	22 (40.7%)
95% CI for Response Rates	(0.00, 97.50)	(15.81, 100.00)	(44.17, 72.42)	(45.03, 72.43)
Complete Response (CR)	0	0	4 (7.8%)	4 (7.4%)
Partial Response (PR)	0	2 (100.0%)	26 (51.0%)	28 (51.9%)
Stable Disease (SD)	0	0	8 (15.7%)	8 (14.8%)
Progressive Disease (PD)	1 (100.0%)	0	3 (5.9%)	4 (7.4%)
Non CR/PD	0	0	3 (5.9%)	3 (5.6%)
Missing or unevaluable	0	0	7 (13.7%)	7 (13.0%)



Note: Patients could be NE if they had an unconfirmed PR occurring before Day 35. PD could occur if the patient had a new lesion appear. The analysis shown in this waterfall plot excludes 6 patients with missing SLD change from baseline; 1 not estimable, 3 non-measurable (with non-CR/non-PD) and 2 with a best overall response of NE in Cycle 1 without a post-baseline scan.

Figure 21: Waterfall Plot: Best Percent Change from Baseline in Tumor Sum (BICR Assessment), NTRK Efficacy Evaluable Analysis Set (CCOD 31 May 2018)

DOR

Table 58: Kaplan-Meier Event-Free Rates for Duration of Response, BICR Assessment (NTRK Efficacy Evaluable Analysis Set), enrolled up to Nov 30, 2017 - CCOD: OCT 31 2018

	ST01 (N=2)	ST02 (N=30)	Total (N=32)
Patients included in analysis	2 (100.0%)	30 (100.0%)	32 (100.0%)
Patients with event (%)	1 (50.0%)	17 (56.7%)	18 (56.3%)
Earliest contributing event			
Disease Progression	1	13	14
Death	0	4	4
Patients without event (%)	1 (50.0%)	13 (43.3%)	14 (43.8%)
Time to event (months) Median			
	NE	12.9	12.9
95% CI for Median	(2.8, NE)	(7.9, NE)	(7.9, NE)
25% and 75%-ile	2.8, NE	6.0, NE	5.8, NE
Range	2.8 to 18.8*	2.8 to 26.0*	2.8 to 26.0*
6 Months	1	21	22
Patients remaining at risk			
Event free probability	0.50	0.73	0.72
95% CI	(0.00, 1.00)	(0.57, 0.89)	(0.56, 0.87)
9 Months			
Patients remaining at risk	1	19	20
Event free probability	0.50	0.66	0.65
95% CI	(0.00, 1.00)	(0.49, 0.83)	(0.49, 0.82)
12 Months			
Patients remaining at risk	1	13	14
Event free probability	0.50	0.55	0.55
95% CI	(0.00, 1.00)	(0.37, 0.73)	(0.37, 0.73)
18 Months			
Patients remaining at risk	1	4	5
Event free probability	0.50	0.34	0.36
95% CI	(0.00, 1.00)	(0.14, 0.54)	(0.17, 0.55)

* Censored, ^ Censored and event
Summaries of Duration of Response (median, percentiles) are Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley.

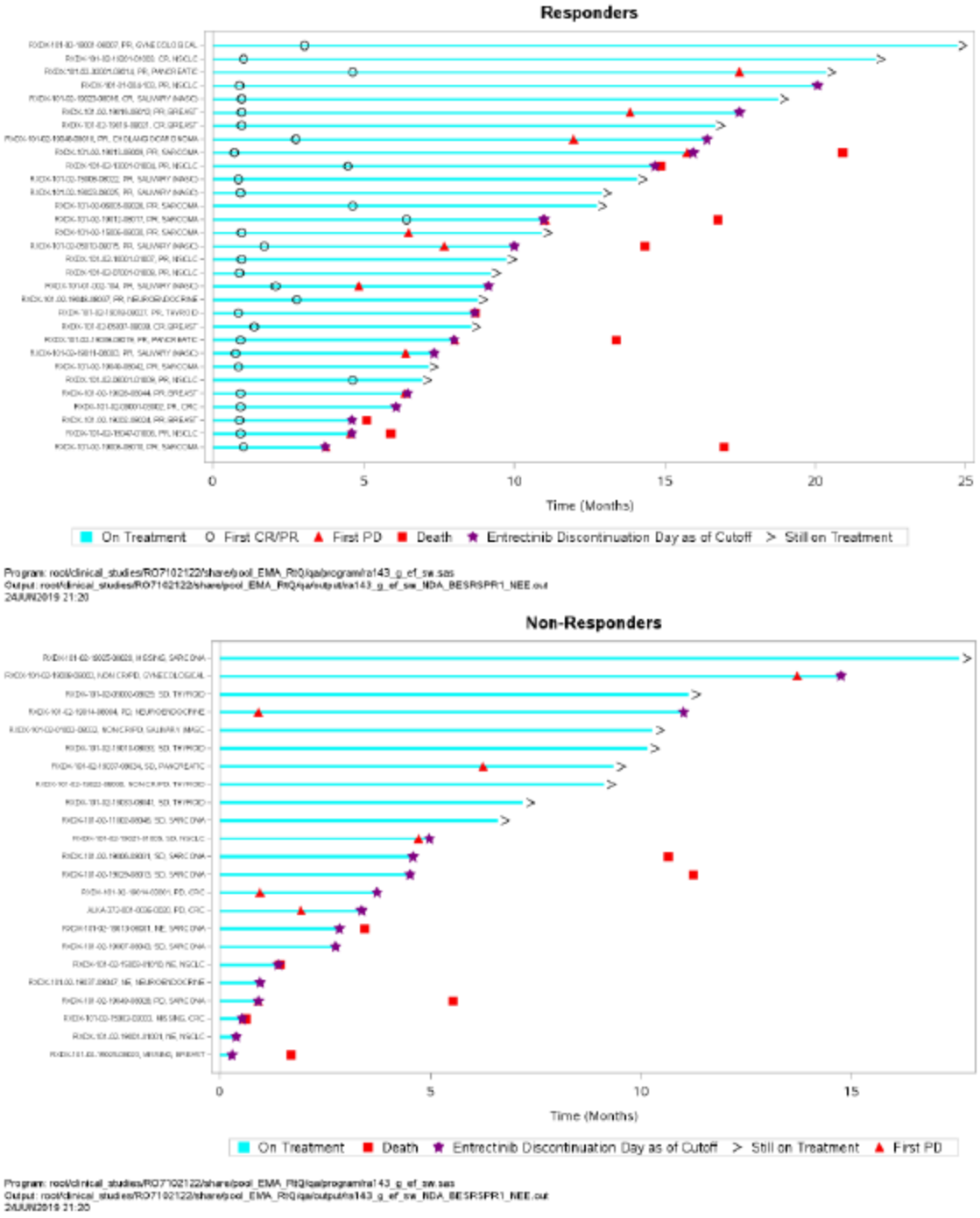


Figure 22: Time on treatment and timing of events for responder and non-responder patients (NTRK efficacy evaluable analysis set; CCOD: 31 May 2018)

Secondary endpoints

Clinical benefit rate (CBR)

In the Efficacy Evaluable Analysis Set, 35 patients had confirmed CR (n=4), PR (n=27), and SD for at least 6 months (n=4), resulting in a CBR of 64.8% (95%CI 50.62, 77.32) at the CCOD 31 May 2018. Stable disease longer than 6 months was achieved by three patients with papillary thyroid cancer and by one with sarcoma (NOS). All 4 subjects have different NTRK gene fusions. At the updated CCOD, stable disease for at least 6 months were 3 (as 1 papillary thyroid cancer patient out of the 4 patients above achieved a PR in the updated analysis).

Time to CNS Progression

Time to CNS progression was 17 months (95% CI: 14.3, NE). This data was confirmed in the updated analysis.It should be noted that patients without CNS lesions present at baseline per the investigator assessment were not required to have scheduled brain scans every 8 weeks.

Progression Free Survival

The K-M estimated median PFS based on the BICR assessment was 11.2 months (95% CI: 8.0, 14.9). Updated PFS was consistent with the K-M estimate of median PFS at the time of the MAA analysis.

Overall Survival

Median OS was 20.9 months (95%CI 14.9, NE), with 16 (29.6%) of patients having a dead event at the CCOD of 31 May 2018. In the updated analysis (CCOD 31 Oct 2018), 3 more patients had died for a median OS of 23.9 months (95% CI: 16.8, NE).

Post-progression treatment: 12/54 patients received post-progression therapy with systemic agents other than continuation of entrectinib.

Intracranial-specific objective response endpoints

Within the NTRK Efficacy Evaluable Analysis Set (n=54), 12 patients had CNS disease at baseline according to investigator. Of those, CNS disease at baseline was confirmed by BICR in 11 patients, in 7 of those disease was measurable.

Systemic efficacy by baseline CNS disease status

Table 59: Summary of Systemic Objective Response Rate and Best Overall Response by BICR Assessment, by Baseline CNS Disease Status as Determined by BICR (NTRK Efficacy Evaluable Analysis Set)

	Baseline CNS Disease Status (by BICR)	
	Yes (n=11)	**No (n=43)**
Objective Response Rate (ORR)		
Responders, n	6	25
ORR (95% CI)[a]	54.5% (23.4%, 83.3%)	58.1% (42.1%, 73.0%)
Best Overall Response (BOR)		
Complete Response, n (%)	0	4 (9.3%)
Partial Response, n (%)	6 (54.5%)	21 (48.8%)
Stable Disease, n (%)	4 (36.4%)	5 (11.6%)
Progressive Disease, n (%)	0	4 (9.3%)
Non CR/PD, n (%)	0	3 (7.0%)
Missing or unevaluable, n (%)	1 (9.1%)	6 (14.0%)

BICR=Blinded Independent Central Review.

[a] Confidence intervals calculated using the Clopper–Pearson method.

Intracranial efficacy in patients with CNS disease at baseline

Table 60: Overview of Intracranial Efficacy in Patients with Baseline CNS Disease Status (BICR Assessment), NTRK Efficacy Evaluable Analysis Set

	All Patients (N=11)	Patients with Measurable Disease (N=7)
Objective Response		
Responders, n	6	4
ORR, % (95% CI)	54.5% (23.38, 83.25)	57.1% (18.41, 90.10)
Best Overall Response		
Patients with CR, n (%)	3 (27.3%)	1 (14.3%)
Patient with PR, n (%)	3 (27.3%)	3 (42.9%)
Patients with stable disease, n (%)	1 (9.1%)	1 (14.3%)
Patients with PD, n (%)	1 (9.1%)	1 (14.3%)
Patients with non-CR/PD, n (%)	2 (18.2%)	0
Patients with missing or unevaluable response, n (%)	1 (9.1%)	1 (14.3%)
Duration of Intracranial Response		
Patients with event, n (%)	2 (33.3%)	1 (25.0%)
Median, months (95% CI)	NE (5.0, NE)	NE (5.0, NE)
Progression-Free Survival		
Patients with event, n (%)	5 (45.5%)	3 (42.9%)
Median, months (95% CI)	14.3 (5.1, NE)	NE (2.8, NE)

BICR=blinded independent central review; CNS=central nervous system; CR=complete response; NE=not estimable; NTRK=neurotrophic tyrosine receptor kinase; ORR=objective response rate; PD=progressive disease; PR=partial response.

Table 61: Intracranial ORR and Duration of Intracranial Response (BICR Assessment) by Prior Brain Radiation Therapy Status in Patients with Solid Tumors Harboring NTRK fusions and CNS Disease at Baseline

	Measureable Disease	Measureable + Non Measureable Disease
	N=7	N=11
Intracranial ORR[a], n (%) (95% CI)		
Brain radiation status and timing relative to study entry		
Total	n=7 4 (57.1%) (18.4%, 90.1%)	n=11 6 (54.5%) (23.4%, 83.3%)
No brain RT	n=3 2 (66.7%) (9.4%, 99.2%)	n=3 2 (66.7%) (9.4%, 99.2%)
≤2 months	n=3 1 (33.3%) (0.8%, 90.6%)	n=3 1 (33.3%) (0.8%, 90.6%)
>2 months	n=1 1 (100.0%) (2.5%, 100.0%)	n=5 3 (60.0%) (14.7%, 94.7%)
No brain RT or brain RT >2 months	n=4 3 (75.0%) (19.4%, 99.4%)	n=8 5 (62.5%) (24.5%, 91.5%)
Median intracranial DoR[c], months (95% CI)[d]		
Brain radiation status and timing relative to study entry		
Total	n=4 NE (5.0, NE)	n=6 NE (5.0, NE)
No brain RT	n=2 NE (NE, NE)	n=2 NE (NE, NE)
≤2 months	n=1 5.0 (NE, NE)	n=1 5.0 (NE, NE)
>2 months	n=1 NE (NE,NE)	n=3 6.7 (NE, NE)
No brain RT or brain RT >2 months	n=3 NE (NE, NE)	n=5 NE (6.7, NE)

RT=radiation therapy.
[a] by RECIST v1.1.
[b] calculated using Clopper-Pearson method.
[c] Kaplan-Meier estimate.
[d] Computed using method of Brookmeyer and Crowley.

Specific information on the type of prior brain radiation therapy received was collected for 3 of the 8 patients who received prior radiation therapy for their CNS disease. Two patients received prior whole brain radiotherapy (WBRT) 406 days and 160 days (>2 months) before their first dose of entrectinib (and had 1 PR, 1 non-CR/non-PD as their best intracranial response by BICR). For the other case where the type of radiation therapy was specified, the patient received WBRT with or without stereotactic radiation therapy (SRT) 28 days before their first entrectinib dose and achieved an intracranial PR by BICR.

Ancillary analyses

Subgroup analyses

ORR and DOR by **tumour types** is presented in table below (firstly by high level grouping of disease, then by specific disease histologies):

Table 62: ORR and DOR (BICR Assessment) by Tumour Type, (NTRK-Efficacy Evaluable Population) – high level grouping - CCOD: 31 OCT 2018

Tumour Type	Patients (N = 74)	ORR		DOR
		n (%)	95% CI	Range (months)
Sarcoma	16	9 (56.3)	(29.9, 80.3)	2.8, 15.1
Non-small cell lung cancer	13	9 (69.2)	(38.6, 90.9)	1.4*, 25.9*
Salivary (MASC)	13	12 (92.3)	(64.0, 99.8)	2.8, 22.1*
Breast cancer (secretory)	4	4 (100)	(39.8, 100)	5.5, 20.2*
Breast cancer (non-secretory)	2	NE, PR	NA	4.2
Thyroid cancer	7	3 (42.9)	(9.9, 81.6)	5.6, 10.9*
Colorectal cancer	7	2 (28.6)	(3.7, 71)	7.9*, 15.2
Neuroendocrine cancers	4	2 (50.0)	(6.8, 93.2)	1.9*, 9.2*
Pancreatic cancer	3	2 (66.7)	(9.4, 99.2)	7.1, 12.9
Ovarian cancer	1	Non CR/PD	NA	26.0*
Endometrial carcinoma	1	PR	NA	26.0*
Cholangiocarcinoma	1	PR	NA	9.3
Gastrointestinal cancer (other)	1	PR	NA	5.6*
Neuroblastoma	1	NE	NA	NA

*Censored
ORR: Objective Response Rate; DOR: Duration of Response; MASC: mammary analogue secretory carcinoma; NA: not applicable due to small number or lack of response; CR: complete response; PR: partial response; PD: progressive disease; NE: not estimable.

Further details on ORR by tumour types are provided below:

- NSCLC: Adenocarcinoma ORR 89% (8/9); Squamous cell carcinoma ORR 0% (0/2); NSCLC NOS ORR 50% (1/2).

- Sarcoma: Angiosarcoma ORR 0% (0/1); chondrosarcoma 0% (0/1); follicular dendritic cell sarcoma 0% (0/1); MPNST 0% (0/1); cervical adenosarcoma 100% (1/1); endometrial stromal sarcoma 100% (1/1); GIST 100% (2/2); Spindle cell 50% (2/4); Sarcoma other 75% (3/4).

- Thyroid: papillary thyroid 25% (1/4); thyroid other 66.7% (2/3).

Response by NTRK gene and gene fusion partner

Table 63: response by NTRK gene (n=54):

Gene Fusion	Total number observed	Number of Responders	Percent Response Rate	Lower 95% CI (%)	Upper 95% CI (%)
NTRK1	22	13	59	43.2	70.8
NTRK2	1	1	0	0	97.5
NTRK3	31	18	58	39.1	75.4

Table 64: Response by Fusion Partner (n=54)

Fusion Partner	Gene	Total number observed	Number of Responders	Percent Response Rate	Lower 95% CI (%)	Upper 95% CI (%)
ETV6	NTRK3	25	17	68	46.5	85.05
TPR	NTRK1	4	4	100	39.76	100
TPM3	NTRK1	4	2	50	6.76	93.24
SQSTM1	NTRK1	2	2	100	15.81	100
LMNA	NTRK1	2	1	50	1.26	98.74
EML4	NTRK3	2	0	0	0	84.19
PEAR1	NTRK1	2	0	0	0	84.19
CD74	NTRK1	1	1	100	2.5	100
CDC42BPA	NTRK1	1	1	100	2.5	100
EPS15L1	NTRK1	1	1	100	2.5	100
PLEKHA6	NTRK1	1	1	100	2.5	100
RBPMS	NTRK3	1	1	100	2.5	100
AKAP13	NTRK3	1	0	0	0	97.5
CGN	NTRK1	1	0	0	0	97.5
ERC1	NTRK1	1	0	0	0	97.5
FAM19A2	NTRK3	1	0	0	0	97.5
KIF7	NTRK3	1	0	0	0	97.5
PDIA3	NTRK1	1	0	0	0	97.5
SQSTM1	NTRK2	1	0	0	0	97.5
TRIM33	NTRK1	1	0	0	0	97.5

Analysis by investigator assessment (CCOD 31 May 2018)

ORR by Investigator: ORR by investigator assessment was 53.7% (39.61, 67.38), with 29 responding patients (CR n=5 [9.3%] PR n=24 [44.4%]).

Concordance between BICR- and investigator-assessed response was 85.1%. Discordance in the time of PD (dates differed by >30 days) was observed for 8 patients (14.8%) (PD by the investigator earlier than by the BICR for 2 patients).

CBR by Investigator: clinical benefit rate was 70.4%.

DOR by Investigator: The median DOR for the 29 responders based on the investigator assessment was 8.3 months (95% CI: 6.2, 14.8).

PFS by Investigator: The median PFS based on the investigator assessment was 10 months (95% CI: 6.5, 13.8).

Patients excluded from the efficacy evaluable analysis dataset

A total of 13 patients were included in the NTRK efficacy non-evaluable analysis set:

- primary CNS tumor (n=6)

- NTRK biomarker ineligibility (n=3)

- comorbidities (n=2)

- ECOG PS>2 (n=1)

- non-measurable disease (n=1)

The overall ORR by BICR of the 13 NTRK non-evaluable subjects was 15.4% (95%CI 1.92, 45.45). The two responding patients corresponded to the two subjects excluded for comorbidities.

Results in primary CNS tumors

Among the 8 subjects with primary CNS tumors, only one achieved an objective response according to RANO criteria, i.e. ORR 12.5% (1/8).

Table 65: Listing of Efficacy of Entrectinib in Adult Patients with Primary Brain Tumours Harbouring NTRK Fusions (CCOD: 31 October 2018)

	Demographic, baseline and disease characteristics					Efficacy parameter (RANO criteria by BICR)			Patient status at CCOD	
Patient ID	Primary brain tumor type	NTRK Gene fusion	Prior lines of therapy (type)	surgery	RT	BOR	DOR (months)	PFS (months)	Discon. treatment (reason)	Discon. study (cause)
Adult Patients with Primary Brain Tumors										
Patient 1	glioneuronal	*BCAN-NTRK1*	0	1	0	–[c]	N/A	0.03	Y (by subject)	Y (by subject)
Patient 2	Glioma	*BCAN-NTRK1*	2 (TMZ)	2	1	PD	N/A	0.95	Y (PD)	Y (death)
Patient 3	Glioma	*DLG1-NTRK3*	1 (TMZ)	2	1	PD	N/A	0.82	Y (PD)	Y (LTFU)
Patient 4	Glioma	*SPECC1L-NTRK2*	1 (TMZ)	2	1	SD	N/A	3.52	Y (PD)	Y (death)
Patient 5	Glioma	*NTRK1*[b]	0 (Chemo)	1	2	PD	N/A	0.59	Y (PD)	Y (death)
Patient 6	Glioma	*SPECC1L-NTRK3*	1 (TMZ)	0	1	PR	2.79	6.34	Y (PD)	Y (death)
Patient 7[a]	Glioma	*CDK5RAP2-NTRK2*	1 (TMZ)	2	1	SD	N/A	2.66	Y (AE)	N
Patient 8[a]	Glioma	*NACC2-NTRK2*	1 (Chemo)	2	1	PD	N/A	0.76	Y (PD)	Y (death)

AE, adverse event; BICR, linded independent central review; LTFU, lost to follow-up; N/A, not applicable; RT, radiation therapy.

[a] Adult patients enrolled after 30 November 2017, the enrolment cutoff used for the MAA submission.

[b] Fusion partner was not reported.

[c] Patient had missing RANO assessments.

[d] Response ongoing at time of CCOD.

Patients Reported Outcomes (PROs)

PROs were only evaluated in STARTRK-2 (n=51), and were not included in the integrated efficacy analysis. The completion rates for QLQ-C30, QLQ-LC13 and QLQ-CR29 were high at baseline (94.1%, 100%, and 100%, respectively) and the completion rate remained high (≥80%) at most study visits. It was 55% at the EOT visit (QLQ-C30). At baseline, patients reported moderate-to-high functioning scores for QLQ-C30. While receiving entrectinib, patients tended to maintain or improve on high baseline HRQoL (mean changes ranging from -4.17 to 9.72 on the GHS). For functional scales (e.g., physical functioning, role functioning), patients continued to report moderate-to high scores at most study visits, with a trend towards clinical improvement, with the exception of cognitive functioning, which while maintaining overall its high baseline value, trended towards some worsening over time above the threshold of 10-points (worst mean change score of -11.11 at Cycle 20 Day 1). Patients with NSCLC (n=9) and those with mCRC (n=3) reported low symptom burden at baseline at and at most study visits throughout the study.

Molecular analyses

Table 66: Summary of Enrollment by Assay

Efficacy Evaluable Analysis Set	No. of patients	Enrollment assay		
		Pharos	F1/F1H	Others
NTRK1/2/3	54	20	16	18

F1/F1H =FoundationOne (F1)/FoundationOne Heme (F1H)

Others= other local test (>35 enrollment assays in total; most tests contributed 1-2 patients each)

Co-development of the NGS FoundationOne CDx (F1CDx) with entrectinib is underway. This assay detects several alteration types (fusion, single nuvleotide varians, copy number variants, insertion/deletion), and tests coexisting oncodrivers (324 genes). F1CDx does not have coverage of NTRK3 intronic regions, while the most common rearrangement gene partner of NTRK3, which is ETV6, is covered by F1CDx.

There are no data on concordance/discordance of molecular results in primary vs metastatic sites.

Concomitant genetic alterations:

Full molecular analysis is available for 40 out of 93 patients with NTRK fusion positive tumour enrolled up to 31 October 2018. Indeed, those subjectects were tested for co-occurrent molecular alteration per local screening process. Overall, 33/40 (82.5%) have detectable molecular alteration (single nucleotide variant, amplification, deletion/loss, rearrangement) while in 7 no concomitant alteration reported. According to the Applicant, such alterations apparently are not driver/ do not represent clinically actionable biomarker, and no relevant patterns of association of specific molecular alterations with e.g. tumor types, NTRK mutated gene, fusion gene, emerged. ORR in patients with tumor harbouring other mutations is reported to be 50%, and without other mutations was 86%. In subjects not tested for other mutations, ORR was 63%. All CIs are overlapping, with non-significant p-values for association.

Table 67: Co-occurring Molecular Alterations Identified with NTRK Fusions (excerpt - only the 40/93 patients tested for molecular alterations are shown)

Patient ID	Tumor Type	Fusion Partner	Concomitant Oncodriver Assessed? (Y/N)	Other Molecular Alterations Identified - Single Nucleotide Variants	Other Molecular Alterations Identified - Amplifications	Other Molecular Alterations Identified - Deletions/Loss	Other Molecular Alterations Identified - Rearrangement	BOR
	Salivary (MASC)	ETV6-NTRK3	Y	NONE REPORTED	DDR2; MCL1; RIT1; CDC73; MDM4; IKBKE; IL10; H3F3A; PARP1; RFWD2; FH; AKT3; NTRK1; SDHC; HIST2H3D; HIST2H3C	PTPRS; TNFAIP3; PRDM1; FYN; EPHA7; BLM; IGF1R	NONE REPORTED	PR
	NSCLC	NTRK1-SQSTM1	Y	NONE REPORTED	NONE REPORTED	NONE REPORTED	NONE REPORTED	PR
	Salivary (MASC)	ETV6-NTRK3	Y	NONE REPORTED	MYC; PIK3C2B; ABL2; AKT3; NOTCH2; Chromosomes 1q, 7, 8q22.1-24.22	Chromosomes 8p21.1-21.2, 15q26.1-26.2, 22q	NONE REPORTED	NON CR / PD
	NSCLC	CDC42BPA-NTRK1	Y	NONE REPORTED	CDK4; MDM2; FRS2	CDKN2A/B	BRCA1	PR
	NSCLC	ETV6-NTRK3	Y	NONE REPORTED	NONE REPORTED	NONE REPORTED	NONE REPORTED	PR
	CRC	TPM3 - NTRK1	Y	TP53	CCND1	NONE REPORTED	NONE REPORTED	NE
	NSCLC	TPM3 - NTRK1	Y	DNMT3A; TERT	EGFR	NONE REPORTED	NONE REPORTED	NE
	Thyroid	ETV6 - NTRK3	Y	NONE REPORTED	NONE REPORTED	NONE REPORTED	NONE	PR
							REPORTED	
	Sarcoma	TPM3-NTRK1	Y	NONE REPORTED	NONE REPORTED	NONE REPORTED	NONE REPORTED	PR
	Sarcoma	PEAR1-NTRK1	Y	NONE REPORTED	MYC	NONE REPORTED	NONE REPORTED	SD
	Sarcoma	PDIA3-NTRK1	Y	NONE REPORTED	NONE REPORTED	BIRC3	NONE REPORTED	SD
	Salivary (MASC)	ETV6-NTRK3	Y	MET	NONE REPORTED	TP53; ERBB2	NONE REPORTED	PR
	NSCLC	SQSTM1 - NTRK2	Y	TP53	NONE REPORTED	NONE REPORTED	NONE REPORTED	SD
	Sarcoma	PEAR1-NTRK1	Y	EED	NONE REPORTED	CDKN2A/B	NF2	NE
	Salivary (MASC)	ETV6 - NTRK3	Y	TERT	NONE REPORTED	NONE REPORTED	NONE REPORTED	PR
	Thyroid	ETV6-NTRK3	Y	RAC1; NF1	NONE REPORTED	CDKN2A; CDKN2B	NONE REPORTED	PR
	GI - Other	ETV6 - NTRK3	Y	TERT	NONE REPORTED	NONE REPORTED	NONE REPORTED	PR
	Thyroid	TPM3 - NTRK1	Y	TERT; RBM10	NONE REPORTED	NONE REPORTED	NONE REPORTED	NE

	Neuroendocrine	TPM3 - NTRK1	Y	APC	NONE REPORTED	TSC1	NONE REPORTED	PR
	Breast	ETV6-NTRK3	Y	NONE REPORTED	NONE REPORTED	NONE REPORTED	NONE REPORTED	CR
	NSCLC	ETV6-NTRK3	Y	CREBBP; MLL3, TP53	CCND2; RICTOR; FGF10; FGF23; FGF6	NONE REPORTED	NONE REPORTED	SD
	Thyroid	ETV6-NTRK3	Y	APC	NONE REPORTED	NONE REPORTED	NONE REPORTED	Non CR / PD
	Salivary (MASC)	ETV6-NTRK3	Y	NONE REPORTED	NONE REPORTED	NONE REPORTED	NONE REPORTED	PR
	Sarcoma	TPM3 - NTRK1	Y	PIK3CA; CAMTA1; LMNA; NGF; NTRK1; PTGIS; SLC6A3; TBX2; XIRP2	NONE REPORTED	CDKN2A	NONE REPORTED	PR
	Sarcoma	EML4-NTRK3	Y	NONE REPORTED	NONE REPORTED	CDH1; CDKN2A/B	NONE REPORTED	NA
	Breast	CGN-NTRK1	Y	PIK3CA; CHEK2	NONE REPORTED	CDH4	NONE REPORTED	NA
	Breast	ETV6-NTRK3	Y	NONE REPORTED	NONE REPORTED	CDKN2A/B; p14ARF, CDKN2B	NONE REPORTED	PR
	Sarcoma	AKAP13-NTRK3	Y	NF1	HGF; RPTOR	CDKN2A/B	FANCA; IGH; LRP1B; NCPR2	SD

	Thyroid	TRIM33-NTRK1	Y	TERT; TET2	NONE REPORTED	NONE REPORTED	NONE REPORTED	SD
	Pancreatic	ERC1-NTRK1	Y	TP53	CCND1; MYC; FGF19; FGF3;FGF4;GATA6	NONE REPORTED	NONE REPORTED	SD
	Neuroendocrine	SQSTM1-NTRK2	Y	NONE REPORTED	NONE REPORTED	NONE REPORTED	NONE REPORTED	NE
	Pancreatic	TPR-NTRK1	Y	BCOR	NONE REPORTED	CDKN2A/B	NONE REPORTED	PR
	Sarcoma	ZNF382 - NTRK1	Y	NONE REPORTED	NONE REPORTED	CDKN2A/B; CDKN2C; FAF1	NONE REPORTED	NE
	NSCLC	SQSTM1-NTRK1	Y	GNAS	NONE REPORTED	NONE REPORTED	NONE REPORTED	PR
	Cholangiocarcinoma	PLEKHA6-NTRK1	Y	PTEN	BRAF; MYC	NONE REPORTED	NONE REPORTED	PR
	Neuroendocrine	ETV6-NTRK3	Y	NONE REPORTED	NONE REPORTED	NONE REPORTED	SLIT2	PR
	NSCLC	TPM3 - NTRK1	Y	AXL; BRD4	NONE REPORTED	CDKN2A; MLH1	NONE REPORTED	CR / PD
	Head and Neck	ETV6 - NTRK3	Y	NONE REPORTED	MCL1; GBA; RIT1; NTRK1; PVRL4; SDHC; DDR2; CDC73; UBE2T; PIK3CB;	NTRK3; FANCI; IDH2; BLM; IFG1R	NONE REPORTED	PR

					MDM4; PTPN14; H3F3A; EGLN1; FH; EXO1; AKT3; NFKBIZ; FOXL2; ETV5			
	Thyroid	TPR - NTRK1	Y	LRP1B; TERT	NONE REPORTED	NONE REPORTED	NONE REPORTED	PD
	Breast	MYO5A - NTRK3	Y	TP53	PAK1	CDKN2A; CDKN2B	NONE REPORTED	NE

BOR = best overall response; CR = complete respose; MASC = mammary analogue secretory carcinoma; NSCLC= non-small cell lung cancer; PD = disease progression; PR = partial response.

Cases are however reported where NTRK fusion was concurrent with an oncogenic driver. A total of 3 patients are described (excluded from the primary analysis): a NSCLC with EGFR T790M (PD as BOR), one patient with pancreatic cancer and KRAS G12R (SD as BOR), and a breast cancer with ALK fusion (apparently not among the responders).

In ctDNA analyses, two driver mutations were found in PIK3CA – R88Q and C420R.

Secondary resistance:

In the NTRK efficacy evaluable population, overall 4 tumor tissue samples obtained at progression are available to date. NTRK1 G595R mutations in two patients and one NTRK3 G623R mutation from another patient were observed. No clear resistance mechanism was identified in the fourth patient.

Paired plasma samples at baseline and at progression are being collected in STARTRK-2 patients and circulating tumor DNA (**ctDNA**) analysis on the FoundationOne Liquid (~70 gene NGS test) was peerformed. To date of the 54 NTRK fusion positive MAA patient population, 29 had an available sample at progression. For NTRK1/3, 10 patients had a detectable solvent front mutation from the end of treatment sample that was not detected in their pre-treatment sample (10/29; 34.5%), which included NTRK1 G595R, NTRK1 G595R, NTRK3 G623E, NTRK3 G623K and NTRK3 G623R. Additional short variant alterations were detected in 1 each of KRAS, BRAF, ERBB2, RET, MET and EGFR. For ERBB2, RET, MET and EGFR, the Sponsor believes these are variant of unknown significance. For BRAF and KRAS, the alteration at end of study is considered oncogenic by the Applicant, V600E and G12D respectively.

Summary of main study

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

Table 68: **Summary of efficacy for NTRK fusion-positive solid tumor pooled analysis**

Title: NTRK Integrated analysis (evaluation of efficacy and safety of oral entrectinib in patients with NTRK fusion-positive solid tumor)	
Study identifier	Integrated efficacy analysis of the NTRK fusion-positive solid tumor patients treated within 3 studies: - RXDX-101-02 (STARTRK-2) - ALKA-372-001 (ALKA) - RXDX-101-01 (STARTRK-1)
Design	Pooled analysis. All patients received entrectinib. The design of the 3 studies was: - STARTRK-2: phase 2 global single arm open label multicenter basket study of oral entrectinib at the RP2D in patients with solid tumor with NTRK, ROS1 or ALK gene fusions. - ALKA and STARTRK-1: phase 1 single arm open label studies of oral entrectinib in patients with solid tumor with NTRK, ROS1 or ALK molecular alterations.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable not applicable not applicable
Hypothesis	Assuming the true ORR by BICR was 60%, a sample size of 56 patients yield a 95% 2-sided CI with precision ±14% that exclude a lower limit of 30%.		
Treatments groups	Entrectinib		Entrectinib orally at or above the RP2D of 600 mg once daily
Endpoints and definitions	Primary endpoints	Objective response rate (ORR)	Proportion of patients with confirmed CR or PR (responders) per RECIST 1.1 by BICR (a confirmed response was a response that persisted on repeat-imaging ≥4 weeks after initial documentation of response)
		Duration of response (DOR)	Time from the date of first objective response (either CR or PR, based on RECIST 1.1 by BICR) to first documentation of radiographic disease progression or the date of death due to any cause, whichever was earlier.
	Secondary endpoints	Time to CNS Progression	Time from first dose of entrectinib to first documentation of radiographic CNS disease progression (i.e. new CNS lesion or progression in any CNS lesion per RECIST 1.1 by BICR) or death due to any cause.
		Progression-Free Survival (PFS)	Time from first dose of entrectinib to first documentation of radiographic disease progression per RECIST v1.1 by BICR or death due to any cause.
		Overall Survival (OS)	Time from the first dose of entrectinib to the date of death due to any cause.
	Intracranial specific endpoints (evaluated in the subpopulation with CNS disease at baseline)	Intracranial Objective Response Rate (IC-ORR)	Proportion of patients with confirmed CR or PR in the CNS lesion(s) per RECIST 1.1 by BICR (intracranial responders). Confirmed response persisted on repeat-imaging ≥4 weeks after initial documentation of response.
		Intracranial-Duration of Response (IC-DOR)	Time from the date of first intracranial response to first documentation of radiographic CNS disease progression (per RECIST 1.1 by BICR) or date of death due to any cause, whichever was earlier.
		Intracranial Progression-Free Survival (IC-PFS)	Time from first dose of entrectinib to first documentation of radiographic CNS disease progression (i.e. new CNS lesion or progression in any CNS lesion per RECIST 1.1 by BICR) or death due to any cause.
Database lock	Patients enrolled up to 30 November 2017 Updated Clinical cut off date (CCOD) 31 Oct 2018		

Results and Analysis

Analysis description	**Updated Analysis (primary analysis was on n=54 patients)**	
Analysis population and time point description	Other: NTRK fusion positive efficacy population (pooled from 3 studies) Patients must met all the following criteria: - Have tumors that harbor an NTRK gene fusion - Received at least 1 dose of entrectinib - Has an extracranial solid tumor (i.e. exclusive from primary brain tumor) - Measurable disease at baseline as assessed by investigator - Not treated previously with a TRK inhibitor - Had at least ≥6 months follow up	
Descriptive statistics	Treatment group	entrectinib
	Number of subject	**74**

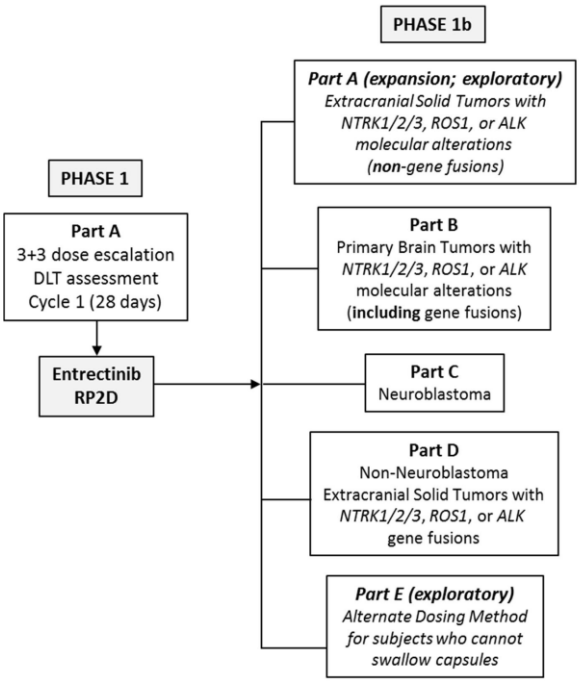
	ORR rate (95%CI)	**63.5%** (n=47) **(51.5, 74.4)** CR 6.8% (n=5); PR 56.8% (n=42)	
	DOR Patients with event (%) median (months) (95%CI)	21 (44.7%) **12.9** **(9.3, NE)**	
	Time to CNS progression Patients with event (%) Median (months) (95%CI)	27 (36.5%) **16.8** **(14.3, NE)**	
	PFS Patients with event (%) median (months) (95%CI)	41 (55.4%) **11.2** **(8.0, 15.7)**	
	OS Patients with event (%) median (months) (95%CI)	24 (32.4%) **23.9** **(16.0, NE)**	
	Number of subject with CNS disease at baseline by BICR	**8** (measurable disease)	**16** (all subjects)
	IC-ORR rate (95%CI)	**62.5%** (n=5) **(24.5, 91.5)**	**50.0%** (n=8) **(24.7, 75.4)**
	IC-DOR Patients with event (%) median (months) (95%CI)	2/5 (40%) **NE** **(5.0, NE)**	4/8 (50%) **8.0** **(6.7, NE)**
	IC-PFS Patients with event (%) median (months) (95%CI)	4 (50.0%) **10.1** **(2.8, NE)**	10 (62.5%) **8.9** **(5.9, 14.3)**
Notes	**Pediatric patients**: 7 patients with NTRK fusion enrolled at the CCOD (31 Oct 2018), 6 evaluated for efficacy at the CCOD, 1 SR, 4 PR, 1 PR (not confirmed yet at the CCOD) from STARTRK-NG **Primary CNS tumor**: 8 patients, 1/8 (12.8%) responded by RANO criteria.		

Clinical studies in special populations

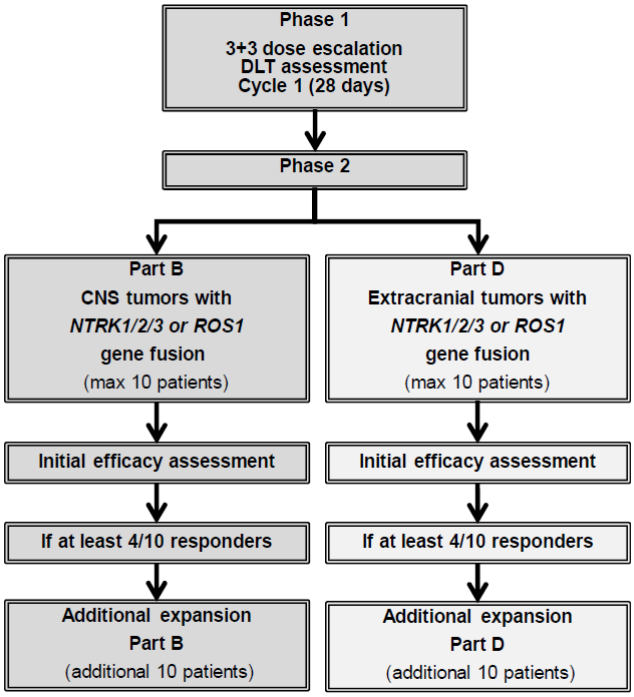
STARTRK-Next Generation (NG) (paediatric study)

This study is a 5-part dose escalation (phase 1) and dose expansion (phase 1b) study. Only the dose escalation phase 1 part A has been included in the submission.

A Phase 1/1b, Open-Label, Dose-Escalation and Expansion Study of Entrectinib (RXDX-101) in Children and Adolescents with Recurrent or Refractory Solid Tumors and Primary CNS Tumors, with or without TRK, ROS1, or ALK Fusions.



The updated protocol design as per protocol version 6 (dated 21 May 2019) is as follow. Part A, C and E have been closed, while Part B and D are still opened and enrolling (see figures below):



CNS=central nervous system; DLT=dose-limiting toxicity; max=maximum.

Figure 23: Updated protocol design as of amendment version 6 (Phase 1/2)

Methods

Study participants

The Study enrols children, adolescents, and young adult patients with relapsed or refractory extracranial solid tumors (Phase 1; Part A. i.e. regardless molecular alteration), with additional expansion parts (Phase 1b).

Prior to 25 October 2018 (Protocol v.5) there was no requirement for tumour to carry a fusion in NTRK, ROS1 or ALK.

From protocol version 6, tumor should harbor NTRK1/2/3 or ROS1 gene fusions (enrollment of ALK fusion positive tumor will be discontinued) as determined locally by an appropriately validated assay performed in a CLIA-certified or equivalently-accredited diagnostic laboratory, or centrally by a Foundation Medicine (FM) Clinical Trial Assay. For patients enrolled via local molecular testing, submission of archival tumor tissue for independent central testing at FM is required.

Treatments

Phase I part A (dose escalation): Entrectinib was administered orally with food, once daily, in repeated 4-week cycles. The doses levels were: 250 mg/m2, 400 mg/m2, 550 mg/m2, 750 mg/m2. (F2B formulation was administered in the first dose level, F1 for the subsequent dose levels).

Phase Ib part B, C, D: Entrectinib doses at the pediatric RP2D determined in Part A.

Phase Ib part E: entrectinib initially dosed at a -1 dose level de-escalation from the RP2D established in Part A. In part E, entrectinib should be mixed with age-appropriate soft food or liquid and consumed with fat-containing food.

According to protocol version 6, in Parts B and D Phase 2 Portion two formulations will be used (i.e., F06 and F1) based upon the patient's ability to swallow. An age-appropriate formulation will be introduced in the future. The recommended dose of 300 mg/m2 with F06 for pediatric patients who can swallow intact capsules. Based on clinical and PK data, patients in STARTRK-NG study will receive entrectinib as follows:

Table 69: Revised recommended dosing per BSA category

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*

BSA =body surface area.

Sample size

Phase 1 (Part A escalation): Planned approximately 6 – 30 patients.

Phase 1b (Part B [Primary Brain Tumors; Gene Fusions] and D [Non-Neuroblastoma Extracranial Solid Tumors with NTRK1/2/3, ROS1, or ALK Gene Fusions]): 2-stage sequential testing. A true response rate of 20% or less is considered insufficient to warrant further study, whereas a true response rate of 40% or more is considered worthy of further study. The number of subjects evaluated in each stage and the minimum number of responders needed to meet the primary endpoint were determined based on a sequential testing technique with at least 80% power and 1-sided $\alpha = 0.025$. The first stage enroll

up to 13 subjects per basket. If successful, up to additional 49 subjects are enrolled into the second stage.

Phase 1b (Part C [neuroblastoma]): A Simon's two-stage design. Stage 1 enroll 13 evaluable subjects. If there is one or more responder, then accrual can continue to Stage 2, enrolling 7 additional subjects for a total of 20 evaluable subjects. If there are 3 or more responders, then there is sufficient evidence of efficacy to warrant further study. This rule has 90% power, with alpha = 0.074, to reject a null hypothesis that the response rate is < 5% compared to an alternative hypothesis that it is > 25%. The expected sample size is 14.82, and the probability of early termination is 0.599.

Phase 1b (Part A [expansion], B [non gene fusion], E): subjects not assessable for efficacy.

Objectives

Primary objective: to determine the MTD or RP2D of entrectinib in pediatric patients (children and adolescents) with relapsed or refractory solid tumors (Phase 1 Part A).

Secondary objectives: safety, PK, systemic efficacy (ORR, DOR, TTR, CBR, PFS in parts A [expansion], C and D), intracranial efficacy (intracranial ORR, DOR, TTR and CNS-PFS in parts B and D).

Exploratory Objectives: molecular analyses.

Statistical methods

No formal statistical hypothesis testing for Phase 1 (Part A) portion was planned. Efficacy, PK, and safety data were summarized using descriptive statistics. A "3+3" patient enrollment scheme was followed during the dose escalation.

Results

Recruitment

The study (phase 1 part A) was opened in 8 centers in USA. First patient was screened on 02 May 2016. **Conduct of the study**

The protocol of the STARTRK-NG study was amended 5 times since the first version (Version 1) dated 05 November 2015. No patients were enrolled under Protocol Version 1.

Critical and important protocol deviations were reported in 2 patients (12.5%) (not occurred in the patient with NTRK gene fusion evaluated for efficacy) at the CCOD of 31 May 2018.

Baseline data

A total of 17 patients were screened during Phase 1 portion of the study and 1 patient failed screening due to withdrawal of consent. A total of 16 patients were enrolled (3 patients at 250 mg/m2; 3 patients at 400 mg/m2; 7 patients at 550 mg/m2; and 3 patients at 750 mg/m2). Only 3 patients had gene fusions (EML4-NTRK3, TFG-ROS1, DCTN1-ALK). Only those 3 subjects achieve an objective response.

Outcomes and estimation

Primary endpoint: DLT

A total of 15 patients were evaluable for DLTs, of whom 14 patients were <18 years of age. A DLT of Grade 2 blood creatinine increased occurred at 550 mg/m2, and 2 DLTs (Grade 2 dysgeusia and Grade 3 pulmonary oedema) at 750 mg/m2. After the the decision of dose reduction from 750 mg/m2 to 550 mg/m2 was made, additional DLTs of Grade 2 blood creatinine and Grade 3 pulmonary oedema (the latter in the same patient of 750 mg/m2) occurred. Based on STARTRK-NG safety results, the dose

550 mg/m2 was declared as MTD and selected as RP2D for further evaluation in the Phase 1b portion of the study for patients able to swallow capsules.

Summary of efficacy data for entrectinib in paediatric patients with NTRK-gene fusion solid tumour

Table 70: Key Demographics, Baseline Characteristics, and Dosing Information of Patients with NTRK fusion-Positive Tumours Enrolled in Study STARTRK-NG (CCOD: 31 October 2018)

	Patient ID	Age (yr) / sex	Part	Tumor Type	Detected NTRK1/2/3, ROS1 or ALK Gene Alteration	Date of Initial Diagnosis (yyyy-mm-dd)	Extent of Disease at Enrollment	Cohort (starting dose level[mg/m²/d])	Starting Dose (mg)	Current Dose (mg)	Formulation
NTRK Gene Fusions			A	infantile fibrosarcoma	*EML4-NTRK3*	2013-10-21	Metastatic disease	4A (750)	400	100 [a]	F1 intact capsule
			B	epithelioid glioblastoma	*ETV6-NTRK3*	2017-11-27	Locally advanced	Ph1b (550)	400	400	F1 intact capsule
			B	anaplastic ganglioglioma	*EML1-NTRK2*	2018-01-08	Metastatic disease	Ph1b (550)	600	700	F1 intact capsule
			B	CNS Primary ganglioneuroblastoma	*KANK1-NTRK2*	2017-02-21	Metastatic disease	Ph1b (550)	400	500	F1 intact capsule
			E	metastatic melanoma (to the lung)	*ETV6-NTRK3*	2015-01-09	Metastatic disease	Ph1b (400)	300	200	F1 open capsule
			E	high-grade glioma	*TPR-NTRK1*	2016-05-06	Metastatic disease	Ph1b (400)	300	300	F1 open capsule
			E	infantile fibrosarcoma	*ETV6-NTRK3*	2017-08-25	Locally advanced	Ph1b (400)	100	100	F1 open capsule

[a]. Patients had discontinued treatment by CCOD (31 October 2018), the last entrectinib dose the patient received prior to discontinuation is listed as "current dose".

Table 71: Treatment and Efficacy Results of Patients with NTRK Fusion-Positive Tumors Enrolled in Study STARTRK-NG (CCOD: 31 October 2018)

	Starting dose level (mg/m²/d)	Patient ID	Age / sex	Gene Fusion	Tumor type	Treatment Start Date	Duration of Treatment	Investigator Assessment (confirmed)			Retrospective Blinded Independent Central Review Assessment (confirmed)		
								BOR	Clinical Benefit	DOR (months)	BOR	Clinical Benefit	DOR (months)
NTRK Gene Fusions	*NTRK*												
	750			*EML4-NTRK3*	infantile fibrosarcoma	2017-10-30	11.14	PR	Y	9.101	PR	Y	9.265
	550			*ETV6-NTRK3*	epitheloid glioblastoma	2018-04-16	6.54[a]	CR	Y	3.713	CR	Y	3.713
	550			*EML1-NTRK2*	anaplastic ganglioglioma	2018-07-09	3.78 [a]	PR	Y	1.873	PR	Y	1.840
	550			*KANK1-NTRK2*	CNS primary ganglioneuroblastoma	2018-10-03	0.95 [a]	-[b]					
	400			*ETV6-NTRK3*	metastatic melanoma (to the lung)	2017-12-12	10.64 [a]	PR	Y	6.472	PR	Y	6.472
	400			*TPR-NTRK1*	high-grade glioma	2017-12-20	10.38 [a]	PR	Y	6.538	PR	Y	6.439

	Starting dose level (mg/m²/d)	Patient ID	Age / sex	Gene Fusion	Tumor type	Treatment Start Date	Duration of Treatment	Investigator Assessment (confirmed)			Retrospective Blinded Independent Central Review Assessment (confirmed)		
								BOR	Clinical Benefit	DOR (months)	BOR	Clinical Benefit	DOR (months)
	400			*ETV6-NTRK3*	infantile fibrosarcoma	2018-01-22	9.30 [a]	SD[c]	Y		CR	Y	4.698

[a] Patient was still receiving entrectinib treatment at the time of the CCOD.

[b] Patient had not completed their first post-treatment tumour assessment at the time of the CCOD.

[c]. Stable disease was maintained for >6 months, and a partial response was recorded at the last tumor assessment (C10D10), but had not been confirmed by the time of the CCOD.

Elderly patients

Table 72: Elderly Patients (≥65 Years) in the NTRK Efficacy-Evaluable Population (N=74)

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	0	0	0
Non Controlled trials			
ALKA	0/1	1/1	0/1
STARTRK-1	0/2	0/2	0/2
STARTRK-2	15/71	10/71	0/71

Supportive study

Not applicable.

2.5.5. Discussion on clinical efficacy

The Applicant is seeking two separate therapeutic indications for entrectinib: one in NTRK fusion-positive solid tumour and one in ROS1 positive NSCLC.

To support each indication, the Applicant presented two integrated datasets (one for NTRK fusion positive solid tumours [**n=54**], and one for ROS1 positive NSCLC [**n=53**]), obtained by pooling efficacy data of patients with the gene fusion/tumour types of interest from the three adult studies. As per CHMP request, results from updated datasets including additional patients were presented during the procedure (**n=94** for ROS1 NSCLC and **n=74** for NTRK-fusion positive solid tumours).

The paediatric study, relevant for the NTRK indication, was not included in the pooling. Paediatric efficacy data have been presented separately.

Further, a real word comparison of entrectinib vs. crizotinib has been presented as supportive for the ROS1 NSCLC indication.

Design and conduct of clinical studies

In **ALKA,** patients were enrolled and assigned to three different dosing schedule of entrectinib. The primary objective of ALKA study was to determine the first cycle DLTs and the MTD. No DLTs were reported and, consequently, no MTD could be defined based on ALKA study for any of 3 schedules investigated.

STARTRK-1 included a dose escalation, with first cycle DLTs, MTD, and determination of a biologically effective dose and RP2D as primary objectives, and a dose expansion segment. A total of 76 patients were recruited and assigned to 7 cohorts in the dose escalation. Three patients in the 800 mg dose group had 1 DLT each.

Both phase I ALKA and STARTRK-1 studies were interdependent, in that dose escalation decisions in one study affected the conduct of the other one. Based on the overall available data, 600 mg once daily on a continuous daily dosing was declared as the RP2D of entrectinib.

STARTRK-2 was designed to enrol patients based on the results of local or central molecular testing on the baskets NTRK, ROS1, ALK and Non Evaluable, further divided in several sub-baskets. The inclusion/exclusion criteria of the 3 studies ALKA, STARTRK-1 and STARTRK-2 appear overall rather homogeneous. All patients received the RP2D of entrectinib 600 mg once daily continuously in 4-weeks cycles until documented radiographic progression as assessed by BICR, unacceptable toxicity or consent withdrawal.

The primary endpoint was ORR by BICR using RECIST v1.1. Among secondary endpoints, there were DOR, PFS, OS, intracranial tumor response and CNS-PFS, QoL. For each basket evaluable for the primary endpoint, up to 62 patients were expected to be enrolled in the 2-stage sequential testing design (Part A). Through the adopted sample size and stopping rules, if the true response rate was <=20%, the probability of stopping enrollment during the first stage was 75%. Conversely, if the true response rate was >40%, then the probability that enrollment was terminated during the first stage is equal to 17%. Moreover, for the ROS1-Positive, ROS1 Inhibitor-Naïve NSCLC Basket, based on expected response rate to crizotinib, after completion of the two stage design (Part A), the enrollment of additional 90 patients in further study (Part B) was planned to rule out a statistically significant BICR-ORR<=50%, by assuming the true ORR is at least 65%, power of 80% and 1-sided alpha=0.025. The result of the Fisher's Exact Test did not show statistical significant difference in ORR in Part A and Part B.

Results in CSR STARTRK-2 study likely derive from data pooled from Part A and Part B studies, with a statistical analysis objective resembling that of the Part B study. In Part B study, additional patients - respect to Part A study - were planned to be enrolled, with a further integrated analysis of Part A and Part B planned to increase statistical power. The dataset used for analysis in the interim CSR is selected through previous testing.

The study was conducted worldwide and started recruitment on 16 November 2015, and is still ongoing at the time of the opinion.

Efficacy data and additional analyses

<u>ROS1 positive NSCLC</u>

The main core of data presented in the original submission to support the sought indication of entrectinib in patients with ROS1-positive, advanced or metastatic NSCLC is represented by **53 adult patients** with ROS1-inhibitor naïve ROS1-positive NSCLC and measurable disease, treated with at least one dose of entrectinib (at or above the RP2D of 600 mg) and having at least 12 months follow-

up from the time of first response, pooled from the phase 1 studies ALKA and STARTRK-1, and the phase 2 study STARTRK-2 (ROS1 NSCLC Efficacy Evaluable Analysis Set). The median survival follow up was 15.54 months. This dataset was updated during the procedure with a 5 months later clinical cut-off date (median survival follow-up of 20.6 months), which overall confirmed prior results. Later on, the Applicant submitted a larger dataset with **n=94 patients** (median follow-up 20.3 months) with a minimum follow up of 12 months. Data for n=161 patients with a minimum follow up of 6 months have also been submitted.

The integrated analysis was not pre-specified in any of the individual study protocols, but was developed after the start of the STARTRK-2. The eligibility criteria and endpoints in the integrated analysis plan (original dated February 2017) were based on the Phase II STARTRK-2 eligibility criteria and study endpoints.

The molecular characterisation of tumor tissue was determined by several assay methods across the three pooled trials, including locally performed IHC, FISH, qPCR, and NGS, and central NGS testing.

Only patients harbouring gene fusions in NTRK, ROS1, or ALK predicted to translate into a fusion protein with a functional kinase domain were considered to have a positive gene-fusion status, while patients with other types of molecular alterations were not considered to be positive for a gene fusion. The co-occurrence of other oncogenic drivers was not systematically evaluated.

The primary endpoints were ORR according to RECIST 1.1 by BICR (based on confirmed responses), DOR and BOR. Secondary endpoints included PFS, OS, CBR, and time to CNS progression. In addition, intracranial-specific endpoints (IC-ORR, IC-DOR and IC-PFS) were evaluated in the subpopulation presented with CNS at baseline, with the aim of assessing the intracranial activity of entrectinib. ORR by BICR was determined in a prospective manner in the phase II study STARTRK-2, but on a retrospective basis for those patients included in the efficacy-evaluable patient population enrolled in the phase I studies ALKA and STARTRK-1, whose tumor images were reviewed by BICR retrospectively.

Sample size for the integrated efficacy analysis (at least 50 patients were planned) was calculated to guarantee a 95% 2-sided confidence interval for the ORR which excluded a lower limit of 50% considered clinically meaningful. An ORR of 70%, and a precision of 17% were assumed in calculations. Sample size calculation for the integrated analysis was performed when efficacy results from each clinical study included in the integrated efficacy analyses were already partially available (ALKA and STARTRK-1 results were reported by Drilon A et al, Cancer Discov. 2017 Apr), and number of responders in STARTRK-2 trial was closely monitored by the Sponsor's study team to determine if a success or stopping criteria were met. True ORR in integrated efficacy analysis (70%) differed from that hypothesized in Part B of STARTRK-2 (65%), with sensible reduction of needed sample size. The Applicant justified assumption on true ORR in view of the background context that crizotinib was approved. However, some preliminary efficacy results for entrectinib were also already available, and it is not possible to exclude that such data might have also have affected other parameters used in sample size calculation (precision). The exclusion criterion based on a history of prior TKI treatment targeting the same fusion of interest of entrectinib was suggested from results of previous efficacy analyses carried out on data of ALKA and STARTRK-1 studies (Drilon et al. 2017) used in integrated efficacy analysis. Although the rationale of this exclusion criterion based on the lack of response is acknowledged and is fully acceptable in the context of exploratory studies, there are concerns regarding the introduction of possible selection biases when used to select study population from an already collected dataset. The concerns regard the possible selection biases derived from post-hoc exclusion of patients based on their observed response in the study. These concerns can only be overcome by the confirmation of results in an independent prospectively analysed data set including patients enrolled based on the refined criteria.

Six (6) months of follow-up is sufficient to capture the vast majority of responses.

Entrectinib was to be used in patients naive to ROS1 inhibitors. About 35% of subjects did not receive any other prior systemic treatment in the metastatic setting. Treatment with entrectinib was allowed after disease progression if the patient was perceived by the investigator to derive clinical benefit, which occurred in up to half of the patients. However, based on available data it is not possible to evaluate the benefit of post-progression treatment with entrectinib. Treatment should therefore be continued until disease progression or unacceptable toxicity.

In the ROS1 NSCLC Efficacy Evaluable analysis (n=53), ORR was 77.4% (95%CI: 63.79, 87.72), with 3 CRs (5.7%). No durable SDs have been observed. ORR assessed by investigator was overall comparable to BICR. The interpretation of ORR subgroup analysis is hampered by the limited number of patients in most of the subgroups. The main observations are an apparently higher response rate in treatment-naïve patients compared to pre-treated ones, and the lower the ECOG-PS is the lower the response rate. Median DOR by BICR was 24.6 months (95%CI 11.4, 34.8). With 25 (47.2%) subjects with a PFS event, median PFS by BICR was 19.0 months (95%CI: 12.2, 36.6), but shorter by investigator (15.5 months). OS was very immature (9 [17%] patients with OS event), median not yet estimable. The interpretation of time-to-event endpoints in single arm trials is intrinsically limited.

As patients with no CNS metastases documented at screening had brain imaging only when clinically indicated, assessment of CNS progression might be delayed. As a result, the detection of disease progression in the brain could have been potentially underestimated in subjects with no baseline CNS disease, moreover time to CNS progression is difficult to be interpreted. Overall, the first progression occurred intracranially in 36% of subjects who progressed during the study. Higher incidence of progression in the brain as 1st site was observed in patient with baseline CNS disease (65%) compared to patients with no baseline CNS disease (15%). The interpretation of these data is difficult due to the small number of subjects. Furthermore, it is difficult to contextualise such data. In patients with CNS disease at baseline by BICR, while systemic ORR was similar, DOR and median PFS were lower compared to patients without baseline CNS metastases. Although based on a limited number of patients, entrectinib does not appear to dramatically improve the prognosis of subjects with brain metastases. In patients with brain metastases, IC-ORR was 55% (75% in subjects with measurable disease), and about 1 year of median IC-DOR. This confirms the poorer prognosis of patients with baseline CNS metastases.

No responses were achieved in subjects with CNS disease when RT was performed ≥2 months from starting entrectinib however intracranial responses were observed in patients who had brain RT within 2 months from the first entrectinib dose. Acknowledging the limited number of patients, while it is encouraging that intracranial responses are seen in patient who did not have RT before, a possible overestimation of IC-ORR due to subjects with RT within 2 months (i.e. possible effect of RT) cannot be excluded, making difficult to determine the real contribution of entrectinib to the observed IC-ORR. Therefore, the group "No brain RT or brain RT >2 months" is considered to better estimate the intracranial response.

Only 3 patients responded to treatment out of 27 subjects who received entrectinib after other ROS1 inhibitors (3/27=11.1%). Among those subjects, 19 patients experienced CNS-only progression while on crizotinib, and of those 2 subjects responded (RR 10.5%). Thus, the wording of the indication reflects that subjects should not have received prior ROS1 inhibitors.

In order to address the above limitations and in order to further characterise the efficacy of entrectinib in patients with baseline CNS disease as well as to generate some comparative safety data, the MAH should conduct and submit the results of a randomised controlled trial versus crizotinib in treatment naïve ROS1 NSCLC patients (PAES in accordance with the Commission Delegated Regulation (EU) No

357/2014 indent c)). The primary endpoint will be PFS in the subgroup of patients with baseline CNS disease with CNS metastases (see Annex II).

Patient reported outcomes (PROs) were evaluated in the 37 ROS1 NSCLC patients in the context of STARTRK-2. A trend toward symptoms improvement since cycle 2 is suggested in this subset. An apparent declining in cognitive functioning within the first cycles is of concern, due to the Cognitive Disorders reported in clinical trials with entrectinib.

Efficacy results from a larger dataset with n=94 patients (all having at least 12 months of follow-up) were: ORR 73.4% (63.3, 82.0) (11.7% CR and 61.7% PR), median DOR 16.5 months (14.6, 28.6) (52% of patients with DOR event), median PFS 16.8 months (12.0, 21.4) (57% of patients with PFS event), median OS NE (28.3, NE) (26.6% of patients with OS event). In the 34 subjects having CNS metastases by BICR, IC-ORR was 50% (32.4, 67.6), IC-DOR 12.9 months (5.6, 22.1) (65% of patients with IC-DOR event), IC-PFS 7.7 months (4.6, 15.7) (73.5% of patients with IC-PFS event).

A pattern of decreasing efficacy estimates over time has been observed, with an ORR of 79% and a DoR of 24 months in the 53 patients submitted in the original MAA, an ORR of 73% and DoR of 16.5 months in the 94 patients proposed by the applicant, and an ORR of 67% and a DoR of 15.7 months in 161 patients with 6 months of follow-up at CCOD 1 MAY 2019. As this is an application for approval based on pooled data from open-label exploratory studies, no particular pivotal population can be acknowledged. The dataset with 161 patients is considered more relevant as it is larger and a more complete representation of ROS1-positive NSCLC patients treated with entrectinib, and is reflected in section 5.1 of the **SmPC.**

The magnitude of this effect is such that it is expected to result in clinically relevant effects.

A comparative analysis of the integrated clinical data from ROS1-positive NSCLC patients treated with entrectinib versus real world data (RWD) from matched ROS1-positive NSCLC patients treated with crizotinib extracted from the US Flatiron Database was submitted as supportive evidence (study WO40977) with the aim to compensate the lack of a direct comparative data of entrectinib vs crizotinib from a randomized clinical trial. Time to treatment discontinuation was the primary endpoint. The proposed RW analysis as the only comparative evidence between entrectinib and crizotinib is not considered a robust demonstration of the superiority of entrectinib over the approved agent in ROS1 positive NSCLC ROS1 inhibitor naïve due to important limitation of the study design and real word data collection, and it is not sufficient to change the overall conclusion.

NTRK gene fusion positive solid tumours

The main core of data supporting the sought "site and histology independent" indication of entrectinib in patients with NTRK fusion positive solid tumour, in adults and paediatric patients, is represented by **54 adult patients** with NTRK fusion-positive solid tumour and measurable disease, receiving at least one dose of entrectinib across the three studies ALKA, STARTRK-1, and STARTRK-2 (NTRK Efficacy Evaluable Analysis Set), and having at least 6 months follow-up. This dataset was updated during the procedure with a 5 months later clinical cut-off date. Later on, a larger dataset with **74 adult patients** was submitted.

Primary brain tumors, as well as paediatric patients with NTRK gene fusion positive disease have been excluded from the main analysis and presented separately.

The integrated analyses were not prespecified in the individual study protocols. Considering the rarity of the patient population, an integrated statistical analysis plan was developed to maximize the number of gene fusion-positive patients available for safety and efficacy analyses, including patients from the Phase I studies. Out of a total of 54 patients included in the NTRK integrated efficacy dataset,

only 3 subjects are coming from the phase I trials, while 51 were enrolled in the STARTRK-2 basket study.

In the extended dataset of n=74 patients with NTRK-fusion positive extracranial solid tumor with >6 months of follow up, the overall ORR was 63.5% (95%CI 51.5, 74.4) and median DOR 12.9 months (95%CI 9.3, NE). ORR by tumour type is difficult to interpret as based on a small number of patients in each subgroup. Different tumour types exhibit different ORR, ranging from 0% to 100%. The estimates by tumour types are not robust due to the small sample size of individual subgroups. Although definitive conclusion on efficacy across tumour types cannot yet be reached, the ORR in the overall population does not appear to represent the expected response in each tumour type. Indeed, higher response rates can be observed in MASC (~90%) and breast secretory (100%), both characterized by NTRK-gene fusion. High response rate is also seen in NSCLC (~70%), where although NTRK fusions are rare, several targeted therapy have shown high response rate in NSCLC with molecular alterations. On the contrary, quite low ORR is seen in CRC, which is also confirmed in the updated dataset (~30%). Far limited responses are achieved in the CNS primary tumour (ORR ~10%). The uncertainties on the drug effect according to tumour type have been reflected in the product information (see sections 4.4 and 5.1 of the SmPC).

With more than half of the subjects having a PFS event, median PFS by BICR was 11.2 months (95%CI 8.0, 15.7). Median OS was 23.9 months (95% CI: 16, NE), with about 30% of patients with death event, which is immature to date. The interpretation of time-to-event endpoints in single arm trials is intrinsically limited. Moreover, the impact of treatment on PFS and OS cannot be disentangled from the prognosis of the different tumour types included in the integrated NTRK dataset. In this regard, in the attempt to contextualize results with the prognosis, subgroup analyses by tumour type have been compared with the available SOCs for each disease. Comparison of TTP in relation to post-progression survival has not been provided instead. The interpretation of the results by tumor types is hampered by the very low number of subjects in each subgroup, for some disease only one patient is available. While the results of entrectinib in ORR and PFS could appear as broadly comparable with the available treatment options in later line for each tumor types, the data are far from comprehensive to reach meaningful conclusion. Hence, additional data are being requested as part of specific obligations to the marketing authorisation (see "Additional efficacy data needed in the context of a conditional MA").

CNS metastasis

Median time to CNS progression was 17 months. As patients with no CNS metastases documented at screening had brain imaging only when clinically indicated, assessment of CNS progression might be delayed, therefore time to CNS progression in difficult to be interpreted. None of the patient progressed while on study had intracranial first site of progression, regardless the presence of CNS disease at baseline or prior response to entrectinib. Given the high heterogeneity of the primary tumors included in the dataset, it is difficult to draw conclusion from this data.

Overall, CNS disease at baseline was confirmed by BICR in 11 patients. A similar systemic ORR to entrectinib regardless the presence of CNS disease at baseline by BICR is observed. Six of the 11 patients with CNS disease at baseline by BICR achieved an intracranial objective response, which was observed regardless the use and the timing of prior RT. This is an indication of the activity of entrectinib on CNS metastases, however the number of patients is very limited (see section 5.1 of the SmPC).

Tumour types

A total of 10 tumour types are included in the NTRK integrated efficacy analysis for entrectinib, with sarcoma and NSCLC being the most represented. Among the tumour types included in the analysis, there are rare cancer types highly enriched for NTRK fusion (NTRK gene fusion prevalence of >90%),

such as mammary analogue secretory carcinoma (MASC) of the salivary glands, and secretory breast carcinoma, all cases carrying ETV6-NTRK3 gene fusion. Tumour types with an "intermediate" prevalence of NTRK gene fusions (5%-25%) represented were papillary thyroid carcinoma and GIST. Other tumour types included are more common tumours having a low prevalence of NTRK fusions (<1%). Gene fusions mostly involved NTRK3 gene followed by NTRK1, while NTRK2 appears rarely. The most common gene fusion partner was ETV6-NTRK3.

Previous therapy

The majority of patients had received a previous anticancer systemic therapy in any setting, mostly chemotherapy. Approximately 25% of subjects received entrectinib as first line systemic treatment in the metastatic setting, however most of the patients received entrectinib after the standard drugs indicated in each disease administered in the neoadjuvant/adjuvant setting. 12/54 patients received anticancer treatment post-progression. However none of the enrolled patients received prior NTRK inhibitors and this was reflected in the wording of the indication (see section 4.1 of the SmPC).

Surgical resection

It is acknowledged that some patients presenting with a disease in which cure through surgery is the therapeutic goal such as locally advanced infantile fibrosarcoma, could have a better outcome with cytoreduction of the tumour with larotrectinib followed by surgical resection, thus avoiding disfiguring amputation and permitting limb salvage. This justifies the inclusion of the following criterion "where surgical resection is likely to result in severe morbidity" in the wording of the indication (see section 4.1 of the SmPC).

Concomitant genetic mutations

The molecular characterization of tumours to detect NTRK gene fusion has been performed by several assay methods (IHC, FISH, RT-PCR, NGS) locally, or centrally (NGS Trailblaze Pharos platform). Based on Foundation One data as well as from available entrectinib data, it appears that concomitant genetic mutations occurr frequently in tumour with NTRK fusion, but in most of the cases they are not driver/ have no clinically actionable biomarker. Full molecular analysis is currently available for 40 out of 93 patients with NTRK fusion positive tumour enrolled up to 31 October 2018. Overall, 33/40 (82.5%) have detectable molecular alteration (single nucleotide variant, amplification, deletion/loss, rearrangement). Relevant patterns of association of specific molecular alterations with e.g. tumour types, NTRK mutated gene, fusion gene, apparently do not emerge. No statistical association between entrectinib response and the presence of additional molecular alteration was found. Response rate according to presence/absence of other molecular alteration (50% with, 86% without) is difficult to interpret, due to the limited number of patients tested and the presence of other confounding factors, such as the heterogeneity in term of tumour types/histologies. The frequent presence (90%) of concomitant molecular alteration was shown also from NGS analysis using ctDNA ran on a ~70-gene cancer related test (FOneLiquid). The response was apparently not driven by the presence of molecular alterations. Data are still limited to draw conclusion, though, and further data on tumour genomic profiling by plasma and/or tissue will be submitted post authorisation (see SOB). With regards to gene fusion partner, with the exception of ETV6 (25 patients), there are too few patients within each fusion partner (range 1-4) to conclude on response by fusion partner. The co-development of the FoundationOne CDx (F1CDx) with entrectinib is underway, and any patient who is tested by F1CDx will obtain a comprehensive genomic profile.

Secondary resistance

Available data on secondary resistance include 4 tumour tissue samples obtained at progression, in which NTRK1 G595R mutation was observed in two patients and one NTRK3 G623R mutation observed in another patient. No clear resistance mechanism was identified in the fourth patient. By analysing

ctDNA in paired plasma samples at baseline and at progression with FoundationOne Liquid (~70 gene NGS test), 10/29 patients had a detectable solvent front mutation.

Prior treatments with other drugs that inhibit the same kinases may confer resistance to entrectinib. Resistance mutations in the TRK kinase domain identified following entrectinib discontinuation include *NTRK1* (G595R, G667C) and *NTRK3* (G623R, G623E and G623K). Resistance mutations in the ROS1 kinase domain identified following entrectinib discontinuation include G2032R, F2004C and F2004I. The molecular causes for primary resistance to entrectinib are not known. It is therefore not known if the presence of a concomitant oncogenic driver in addition to an *NTRK* gene fusion affects the efficacy of TRK inhibition. This issue will be further investigated in the context of a specific obligation (see below).

Patient reported outcomes (PROs)

PROs were evaluated in the context of STARTRK-2. At baseline, patients have high HRQoL, as well as good functions and low symptoms burden, and apparently no meaningful changes were reported throughout the study. As observed among analysed ROS1 NSCLC patients, PROs data seems indicate a trend towards a cognitive functioning decline has been flagged and it is still considered consistent with the Cognitive Disorders AEs reported.

Additional expert consultation

Not applicable

Assessment of paediatric data on clinical efficacy

STARTRK-Next Generation (NG) is a phase 1/1b dose-escalation/expansionstudy of entrectinib in children and adolescents with recurrent or refractory solid tumors and primary CNS tumors. In the dose escalation part, the 550 mg/m2 dose level was declared as MTD and selected as RP2D, for patients able to swallow capsules.

Up to 31 October 2018 (enrollment and clinical cut-off date), a total of 29 paediatric patients have been enrolled in STARTRK-NG study, of whom 7 with NTRK fusion-positive tumors, aged from 4 months to 9 years. They presented with different 6 tumor types (4 CNS primary, 2 infantile fibrosarcomaand a metastatic melanoma), mostly with NTRK3 gene fusion. Of those 7 pediatric subjects, 6 were evaluable for efficacy (one had too short follow-up), all achieved an objective response by BICR (2 CR and 4 PR), with DOR ranged between 1.8 and 9.3 months.

Two additional children with NTRK fusion positive solid tumor received entrectinib in the context of compassionate use programme, a 6 years old male with high grade astrocytoma and a 1.5 years old male with infantile fibrosarcoma, both achieving PR according to investigator assessment.

Although the available efficacy results in paediatric patients appear promising, they have been obtained in a very heterogeneus and small population so they have to be interpreted with caution, and it is difficult to draw conclusion based on such limited data.

The final indication that was considered acceptable includes patients aged 12 to 18 years . No efficacy data for entrectinib in NTRK solid tumour are available in this age group however the PK simulations performed for adolescents within BSA 1.1-1.5 m2 showed that the exposure is within those obtained in adults (see clinical pharmacology). The activity of entrectinib in adolescent is considered established based on extrapolation of data obtained in adult patients with NTRK fusion positive solid tumours.

Additional efficacy data needed in the context of a conditional MA

The Applicant requested a Conditional Marketing Authorisation, providing a justification for CMA for the NTRK fusion positive solid tumors indication only. The following Specific Obligations related to NTRK indication have been proposed, which are considered acceptable.

"Specific Obligation number 1 (SOB-1) by 31 March 2027

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.

These data will allow to more precisely characterize the benefit/lack of efficacy of entrectinib across tumour types, to increase precision of the estimates for ORR and DOR with prospectively collected data an sufficient follow-up.

The current dataset will be expanded with at least 200 additional patients with NTRK fusion positive solid tumours across histology (61 already recruited). Between 9-20 patients for the common tumour types where NTRK fusions are rare (lung cancer, melanoma, colorectal cancer and non-secretory breast cancer) will be enrolled, plus additional adult patients in all other indications, including primary CNS patients. About 30 paediatric patients are planned to be presented within the SOB (i.e. 22-27 patients <12 years and 3-5 patients ≥12 years).

Lack of efficacy within a certain tumour type has been defined as less than 4 responders in a group of sequentially enrolled 13 patients (i.e., ORR <30%), which would trigger information to EMA. If a new or underrepresented tumour type has not reached ≥ 13 patients, the Applicant will continue enrollment of patients with this tumour type until the SOB1 deadline, informing EMA about the recruitment status at the time of the annual renewals. Any additional efficacy analyses results that would have to be done upon request from any other health authority will be also shared with EMA.

The target final date for the SOB is 31 March 2027, projected based on the recruitment rate observed so far and taking into account competitive trials and new therapies. However, an interim safety and efficacy analysis will be also submitted, latest by the end of 2023.

"Specific Obligation number 2 (SOB-2) 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 molecular data available so far are too limited to draw definitive conclusion. Therefore, in order to address uncertainties with regard to several molecular aspects, the Applicant will continue to collect plasma for circulating tumour DNA analysis and tumour tissue when medically feasible, and will use NGS for the analysis. The SOB2 will allow a more precise characterization of entrectinib magnitude of effect across tumours based on biomarker status. Such data can therefore clarify entrectinib activity/response according to NTRK fusion status and partners, concurrent oncogenic driver mutations, and concurrent additional alterations. Data on molecular mechanism of primary and secondary resistance, as well as concordance beteween plasma and tissue molecular data, are also expected from this SOB.

2.5.6. Conclusions on the clinical efficacy

ROS1 positive NSCLC

The available efficacy and safety data support a positive absolute B/R for entrectinib in the treatment of adult patients with ROS1 positive NSCLC not previously treated with ROS1 inhibitor. Uncertainties over efficacy and safety have been alleviated by updated data provided by the Applicant, although still in the context of the intrinsic limitations of pivotal data based on SAT.

Based on indirect comparison, the antitumor activity of entrectinib seems to be comparable to the only currently authorised therapy for ROS1 positive NSCLC. Entrectinib is therefore considered to be a valuable treatment option to be offered to patients with ROS1 positive NSCLC in addition to the approved crizotinib.

The CHMP considers that the efficacy of entrectinib in ROS1+ NSCLC has been established based on the data provided, and the magnitude of this effect is such that it is expected to result in clinically relevant benefit. Furthermore, while data on the CNS activity of entrectinib are encouraging, a further characterisation of efficacy in this subgroup of patients who will develop brain metastases is required post authorisation.

The CHMP considers the following measures necessary to address issues related to efficacy:

PAES: In order to further characterise the efficacy of entrectinib in patients with baseline CNS disease, the MAH should conduct and submit the results of a randomised controlled trial versus crizotinib in treatment naïve ROS1 NSCLC patients. The primary endpoint will be PFS in the subgroup of patients with baseline CNS disease with CNS metastases. The targeted filing of the clinical study report is 2027.

NTRK fusion positive solid tumours

The overall response rate observed in the pooled data set is deemed clinically meaningful even though the estimates by tumour types are not robust due to the small sample sizes of individual subgroups and the limited number of tumour types. The available data suggest that the effect size may vary depending on tumour type, as well as on concomitant genomic alterations. Responses appears durable overall, with median >12 months. A higher degree of uncertainty could be considered acceptable for subjects with no satisfactory treatment options (i.e., for which clinical benefit has not been established, or where such treatment options have been exhausted).

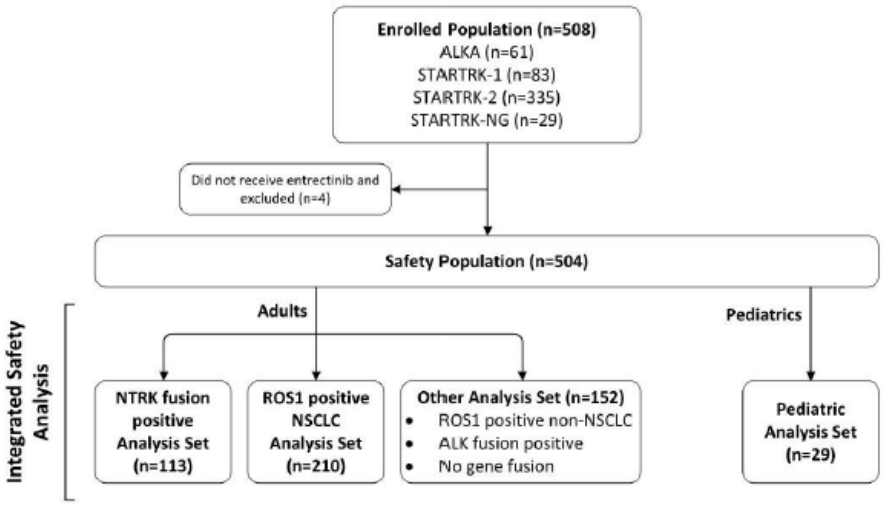
The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- 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 at the latest by Q4 2023.

- 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. Clinical safety

The clinical safety data supporting this application are derived primarily from three ongoing adult studies ALKA, STARTRK-1, and STARTRK-2 and one paediatric Study STARTRK-NG in children adolescents, and young adults. Safety data from the above mentioned studies have been pooled and analysed collectively as the integrated safety population. An overview of these four studies can be found in Table 13 and Figure 24. The analysis set of the safety population submitted in the marketing authorisation application included 355 patients with a CCOD of 31 May 2018. During the procedure, the applicant submitted an updated safety population including 504 patients with a CCOD of 31 October 2018.



ALK; anaplastic lymphoma kinase; NSCLC; non-small cell lung cancer; NTRK; Neurotrophic tyrosine receptor kinase; ROS1; ROS proto-oncogene 1 receptor tyrosine kinase.

Figure 24: Patient Population and Analysis Sets for Integrated Safety Analysis enrolled up to 31 October 2018

In total, 508 patients (including 29 paediatric patients) were enrolled in studies ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG up to 31 October 2018 and comprised the enrolled population. All safety analyses were performed using the integrated safety population, defined as all patients enrolled in studies ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG who received at least one dose of entrectinib, with data collected up to the CCOD (31 October 2018). Of the enrolled population, 4 patients did not receive entrectinib and were therefore excluded from the integrated safety population which consisted of 504 patients; including 475 adult and 29 paediatric patients with solid tumours. In the analyses presented in this report, 4 patients have been reassigned to adult and paediatric groups based on their actual age. Adult patients are now defined as those patients ≥18 years of age while paediatric patients are defined as those patients <18 years of age.

Supportive safety data are also separately provided from the following sources:

– available safety data for an additional 10 paediatric patients from Study STARTRK NG who were enrolled between 1 December 2017 and 31 May 2018.

– safety data for 8 patients treated with entrectinib under a single-case compassionate use program and from 14 adult patients from the Phase I Study RXDX-101-14, which evaluated the potential pharmacokinetic (PK) interaction between entrectinib and midazolam in patients with advanced solid tumours. These supportive patient data were not integrated with the overall safety population because of their different purpose and limited sample size they would contribute to the analysis

– safety data for healthy subjects from 10 dedicated clinical pharmacology studies. These supportive safety data in healthy subjects were not integrated with the overall safety population due to different population, study design, and limited exposure to entrectinib treatment.

Patient exposure

As of the CCOD for the analyses presented in this report, a total of 327 patients (64.9%) in the overall integrated safety population (n=504) had discontinued treatment. The primary reason for discontinuation of entrectinib was disease progression (247 patients [75.5% of those who discontinued]), followed by AEs (44 patients [13.5%]). Other reasons accounted for less than 10% of patients who discontinued treatment; 235 patients out of the 508 enrolled patients had discontinued from the study, 20 patients had completed the study, and 253 patients were still on study. The most common reason for study discontinuation was the death of the patient (50.2% [118/235] of patients who discontinued the study).

Most patients received all their planned doses of entrectinib, with few missed doses; the median number of missed doses was 1.0 (range: 0.0-50.0). The median duration of exposure to entrectinib in the overall integrated safety population, including the 149 additional patients enrolled after 30 November 2017, was 5.5 months (range: 0.0-42.1 months) corresponding to a median of 7.0 cycles (range: 1-92). See the Table below for additional details.

Table 73: Summary of Extent of Exposure to Entrectinib in the Integrated Safety Population (CCOD 31 October 2018)

	NTRK-Adult Patients n = 113	ROS1 NSCLC-Adult Patients n = 210	Other-Adult n = 152	Total Adult Patients n = 475	Pediatric Patients n = 29	All Patients n = 504
Median treatment duration, months (range)[a]	6.4[c] (0.1, 29.7)	7.4 (0.0, 42.1)	2.1 (0.0, 37.0)	5.5[d] (0.0, 42.1)	3.0 (0.2, 17.7)	5.5[e] (0.0, 42.1)
Median no. of cycles (range)	8.0 (1.0, 49.0)	10.0 (1.0, 92.0)	3.0 (1.0, 70.0)	7.0 (1.0, 92.0)	6.0 (1.0, 25.0)	7.0 (1.0, 92.0)
Median no. of missed doses (range)	1.0 (0.0, 36.0)	1.0 (0.0, 25.0)	0.0 (0.0, 19.0)	1.0 (0.0, 36.0)	3.0 (0.0, 50.0)	1.0 (0.0, 50.0)
Mean cumulative dose, mg (SD)	121,987[c] (98,509)	153,029 (160,342)	85,927 (120,806)	124,186[d] (138,482)	75,293 (107,515)	121,355[e] (137,269)
Median dose intensity, % (range)[b]	95.0[c] (33.8, 105.3)	94.9 (13.6, 133.3)	98.6 (12.6, 388.3)	96.5[d] (12.6, 388.3)	94.9 (28.8, 115.1)	96.4[e] (12.6, 388.3)

SD, standard deviation.

[a] Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.

[b] Defined as total cumulative dose actually received/total planned dose x 100%. Factors contributing to dose intensity >100% included patients enrolled during the dose finding portion of the Phase I studies who underwent intra-patient dose escalation after determination of the recommended Phase II dose.

[c] n=110, [d]n=472, [e]n=501. Three patients in the GO40782 (STARTRK-2) study had only one dose with an unknown end date, hence the duration of exposure was unknown.

Adverse events

Almost all patients (99.4%) experienced at least one AE (all grade) during treatment. Most AEs requiring intervention were managed with dose interruption (45.9% of patients) or dose reduction (i.e. 28.2% of patients) (see Table below).

Table 74: Overview of adverse events in the integrated safety population (CCOD: 31 May 2018; safety evaluable population)

Safety Summary, Safety-Evaluable Patients
Protocols: GO40782, GO40783, GO40784, CO40778
Enrollment cutoff: Nov 30 2017, CCOD: May 31 2018, DBL: Jul 31 2018

	NTRK-Adult (N=68)	ROS1 NSCLC-Adult (N=134)	Other-Adult (N=137)	Total-Adult (N=339)	Pediatric (N=16)	Total (N=355)
Patients with AE	68 (100.0%)	134 (100.0%)	135 (98.5%)	337 (99.4%)	16 (100.0%)	353 (99.4%)
Patients with Related AE	61 (89.7%)	125 (93.3%)	123 (89.8%)	309 (91.2%)	16 (100.0%)	325 (91.5%)
Patients with Serious AE	32 (47.1%)	50 (37.3%)	53 (38.7%)	135 (39.8%)	2 (12.5%)	137 (38.6%)
Patients with Related Serious AE	7 (10.3%)	15 (11.2%)	7 (5.1%)	29 (8.6%)	1 (6.3%)	30 (8.5%)
Patients with NCI-CTCAE >= Grade 3 AE	50 (73.5%)	82 (61.2%)	77 (56.2%)	209 (61.7%)	8 (50.0%)	217 (61.1%)
Patients with Related NCI-CTCAE >= Grade 3 AE	29 (42.6%)	46 (34.3%)	32 (23.4%)	107 (31.6%)	3 (18.8%)	110 (31.0%)
Patients with AE Leading to Discontinuation	9 (13.2%)	12 (9.0%)	8 (5.8%)	29 (8.6%)	1 (6.3%)	30 (8.5%)
Patients with Related AE Leading to Discontinuation	3 (4.4%)	6 (4.5%)	5 (3.6%)	14 (4.1%)	0	14 (3.9%)
Patients with AE Leading to Dose Reduction	28 (41.2%)	46 (34.3%)	22 (16.1%)	96 (28.3%)	4 (25.0%)	100 (28.2%)
Patients with Related AE Leading to Dose Reduction	27 (39.7%)	45 (33.6%)	21 (15.3%)	93 (27.4%)	4 (25.0%)	97 (27.3%)
Patients with AE Leading to Drug Interruption	38 (55.9%)	60 (44.8%)	59 (43.1%)	157 (46.3%)	6 (37.5%)	163 (45.9%)
Patients with Related AE Leading to Drug Interruption	21 (30.9%)	37 (27.6%)	28 (20.4%)	86 (25.4%)	4 (25.0%)	90 (25.4%)
Patients with AE Leading to Death	6 (8.8%)	9 (6.7%)	5 (3.6%)	20 (5.9%)	0	20 (5.6%)

Investigator text for AEs encoded using MedDRA version 21.0.
Includes AEs with start date on or after the date of first dose of study treatment and up to and including 30 days after the last dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.

In the overall integrated safety population, the safety profile of entrectinib was generally comparable across all exposure groups with all (100%) patients who were exposed to entrectinib 6 to <12 months and ≥12 months and 98.9% of those exposed to entrectinib <6 months experiencing at least one AE.

Treatment Emergent Adverse Events

TEAEs occurring in ≥10% of patients are summarised in the Table below.

Table 75: Adverse Events Occurring in ≥ 10% of Patients (CCOD: 31 October 2018; safety evaluable population)

MedDRA System Organ Class MedDRA Preferred Term	NTRK-Adult (N=113)	ROS1 NSCLC-Adult (N=210)	Other-Adult (N=152)	Total-Adult (N=475)	Pediatric (N=29)	Total (N=504)
NERVOUS SYSTEM DISORDERS						
DYSGEUSIA	48 (42.5%)	98 (46.7%)	61 (40.1%)	207 (43.6%)	6 (20.7%)	213 (42.3%)
DIZZINESS	44 (38.9%)	90 (42.9%)	44 (28.9%)	178 (37.5%)	4 (13.8%)	182 (36.1%)
PARAESTHESIA	18 (15.9%)	44 (21.0%)	36 (23.7%)	98 (20.6%)	2 (6.9%)	100 (19.8%)
HEADACHE	17 (15.0%)	38 (18.1%)	22 (14.5%)	77 (16.2%)	11 (37.9%)	88 (17.5%)
GASTROINTESTINAL DISORDERS						
CONSTIPATION	49 (43.4%)	103 (49.0%)	53 (34.9%)	205 (43.2%)	11 (37.9%)	216 (42.9%)
DIARRHOEA	43 (38.1%)	75 (35.7%)	43 (28.3%)	161 (33.9%)	8 (27.6%)	169 (33.5%)
NAUSEA	32 (28.3%)	58 (27.6%)	57 (37.5%)	147 (30.9%)	15 (51.7%)	162 (32.1%)
VOMITING	19 (16.8%)	46 (21.9%)	44 (28.9%)	109 (22.9%)	8 (27.6%)	117 (23.2%)
ABDOMINAL PAIN	12 (10.6%)	18 (8.6%)	20 (13.2%)	50 (10.5%)	6 (20.7%)	56 (11.1%)
DYSPHAGIA	10 (8.8%)	26 (12.4%)	15 (9.9%)	51 (10.7%)	0	51 (10.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
FATIGUE	49 (43.4%)	84 (40.0%)	81 (53.3%)	214 (45.1%)	11 (37.9%)	225 (44.6%)
OEDEMA PERIPHERAL	36 (31.9%)	69 (32.9%)	33 (21.7%)	138 (29.1%)	2 (6.9%)	140 (27.8%)
PYREXIA	18 (15.9%)	38 (18.1%)	31 (20.4%)	87 (18.3%)	14 (48.3%)	101 (20.0%)
INVESTIGATIONS						
WEIGHT INCREASED	30 (26.5%)	70 (33.3%)	20 (13.2%)	120 (25.3%)	13 (44.8%)	133 (26.4%)
BLOOD CREATININE INCREASED	33 (29.2%)	54 (25.7%)	27 (17.8%)	114 (24.0%)	14 (48.3%)	128 (25.4%)
ASPARTATE AMINOTRANSFERASE INCREASED	26 (23.0%)	32 (15.2%)	15 (9.9%)	73 (15.4%)	15 (51.7%)	88 (17.5%)
ALANINE AMINOTRANSFERASE INCREASED	27 (23.9%)	30 (14.3%)	9 (5.9%)	66 (13.9%)	15 (51.7%)	81 (16.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
MYALGIA	19 (16.8%)	48 (22.9%)	30 (19.7%)	97 (20.4%)	2 (6.9%)	99 (19.6%)
ARTHRALGIA	21 (18.6%)	43 (20.5%)	29 (19.1%)	93 (19.6%)	3 (10.3%)	96 (19.0%)
MUSCULAR WEAKNESS	12 (10.6%)	25 (11.9%)	19 (12.5%)	56 (11.8%)	6 (20.7%)	62 (12.3%)
BACK PAIN	8 (7.1%)	19 (9.0%)	22 (14.5%)	49 (10.3%)	2 (6.9%)	51 (10.1%)
PAIN IN EXTREMITY	14 (12.4%)	15 (7.1%)	14 (9.2%)	43 (9.1%)	9 (31.0%)	52 (10.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
DYSPNOEA	25 (22.1%)	62 (29.5%)	44 (28.9%)	131 (27.6%)	5 (17.2%)	136 (27.0%)
COUGH	23 (20.4%)	48 (22.9%)	25 (16.4%)	96 (20.2%)	12 (41.4%)	108 (21.4%)
METABOLISM AND NUTRITION DISORDERS						
DECREASED APPETITE	10 (8.8%)	20 (9.5%)	22 (14.5%)	52 (10.9%)	8 (27.6%)	60 (11.9%)
INFECTIONS AND INFESTATIONS						
URINARY TRACT INFECTION	22 (19.5%)	30 (14.3%)	9 (5.9%)	61 (12.8%)	3 (10.3%)	64 (12.7%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
ANAEMIA	40 (35.4%)	45 (21.4%)	40 (26.3%)	125 (26.3%)	17 (58.6%)	142 (28.2%)
VASCULAR DISORDERS						
HYPOTENSION	22 (19.5%)	27 (12.9%)	19 (12.5%)	68 (14.3%)	4 (13.8%)	72 (14.3%)

Adult patients are defined as subject>=18 years of age; Pediatric patients are defined as subjects <18 year of age
Investigator text for AEs encoded using MedDRA version 21.1.
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.
Adverse Events appear in this table if the incidence in the Total arm is ≥10%.
Adapted from t_ae_inc_5P_SE.

Grade 3-5 AEs are summarised in the Table below.

Table 76: Grade 3-5 adverse events with an incidence rate of at least 2% (CCOD: 31 May 2018; safety evaluable population)

Protocols: GO40782, GO40783, GO40784, CO40778
Enrollment cutoff: Nov 30 2017, CCOD: May 31 2018, DBL: Jul 31 2018

MedDRA System Organ Class MedDRA Preferred Term	NTRK-Adult (N=68)	ROS1 NSCLC-Adult (N=134)	Other-Adult (N=137)	Total-Adult (N=339)	Pediatric (N=16)	Total (N=355)
Total number of patients with at least one adverse event	50 (73.5%)	82 (61.2%)	77 (56.2%)	209 (61.7%)	8 (50.0%)	217 (61.1%)
Overall total number of events	136	232	296	664	55	719
INVESTIGATIONS						
Total number of patients with at least one adverse event	13 (19.1%)	27 (20.1%)	19 (13.9%)	59 (17.4%)	6 (37.5%)	65 (18.3%)
Total number of events	16	42	50	108	22	130
WEIGHT INCREASED	9 (13.2%)	11 (8.2%)	3 (2.2%)	23 (6.8%)	0	23 (6.5%)
ASPARTATE AMINOTRANSFERASE INCREASED	2 (2.9%)	4 (3.0%)	5 (3.6%)	11 (3.2%)	1 (6.3%)	12 (3.4%)
ALANINE AMINOTRANSFERASE INCREASED	3 (4.4%)	5 (3.7%)	2 (1.5%)	10 (2.9%)	1 (6.3%)	11 (3.1%)
NEUTROPHIL COUNT DECREASED	0	3 (2.2%)	3 (2.2%)	6 (1.8%)	3 (18.8%)	9 (2.5%)
LIPASE INCREASED	0	1 (0.7%)	6 (4.4%)	7 (2.1%)	0	7 (2.0%)
AMYLASE INCREASED	0	1 (0.7%)	5 (3.6%)	6 (1.8%)	0	6 (1.7%)
LYMPHOCYTE COUNT DECREASED	0	2 (1.5%)	1 (0.7%)	3 (0.9%)	2 (12.5%)	5 (1.4%)
PLATELET COUNT DECREASED	0	0	1 (0.7%)	1 (0.3%)	3 (18.8%)	4 (1.1%)
WEIGHT DECREASED	0	0	0	0	2 (12.5%)	2 (0.6%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	0	0	0	0	1 (6.3%)	1 (0.3%)
WHITE BLOOD CELL COUNT DECREASED	0	0	0	0	1 (6.3%)	1 (0.3%)
RESPIRATORY THORACIC AND MEDIASTINAL DISORDERS						
Total number of patients with at least one adverse event	11 (16.2%)	20 (14.9%)	19 (13.9%)	50 (14.7%)	3 (18.8%)	53 (14.9%)
Total number of events	24	30	26	80	12	92
DYSPNOEA	4 (5.9%)	9 (6.7%)	6 (4.4%)	19 (5.6%)	3 (18.8%)	22 (6.2%)
PULMONARY EMBOLISM	3 (4.4%)	5 (3.7%)	5 (3.6%)	13 (3.8%)	0	13 (3.7%)
HYPOXIA	5 (7.4%)	3 (2.2%)	2 (1.5%)	10 (2.9%)	2 (12.5%)	12 (3.4%)
PLEURAL EFFUSION	3 (4.4%)	4 (3.0%)	4 (2.9%)	11 (3.2%)	0	11 (3.1%)
ACUTE RESPIRATORY FAILURE	2 (2.9%)	0	1 (0.7%)	3 (0.9%)	0	3 (0.8%)
RESPIRATORY FAILURE	0	0	3 (2.2%)	3 (0.9%)	0	3 (0.8%)
PULMONARY OEDEMA	0	0	2 (1.5%)	2 (0.6%)	1 (6.3%)	3 (0.8%)
COUGH	0	0	0	0	1 (6.3%)	1 (0.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
Total number of patients with at least one adverse event	15 (22.1%)	8 (6.0%)	20 (14.6%)	43 (12.7%)	3 (18.8%)	46 (13.0%)
Total number of events	22	15	33	70	6	76
ANAEMIA	13 (19.1%)	4 (3.0%)	18 (13.1%)	35 (10.3%)	3 (18.8%)	38 (10.7%)
NEUTROPENIA	2 (2.9%)	5 (3.7%)	2 (1.5%)	9 (2.7%)	0	9 (2.5%)
FEBRILE NEUTROPENIA	0	0	1 (0.7%)	1 (0.3%)	1 (6.3%)	2 (0.6%)
NERVOUS SYSTEM DISORDERS						
Total number of patients with at least one adverse event	9 (13.2%)	21 (15.7%)	12 (8.8%)	42 (12.4%)	2 (12.5%)	44 (12.4%)
Total number of events	10	26	17	53	3	56
SYNCOPE	3 (4.4%)	4 (3.0%)	1 (0.7%)	8 (2.4%)	1 (6.3%)	9 (2.5%)
HYPERSOMNIA	0	0	0	0	1 (6.3%)	1 (0.3%)
INFECTIONS AND INFESTATIONS						
Total number of patients with at least one adverse event	11 (16.2%)	18 (13.4%)	13 (9.5%)	42 (12.4%)	1 (6.3%)	43 (12.1%)
Total number of events	12	23	29	64	2	66
PNEUMONIA	4 (5.9%)	5 (3.7%)	5 (3.6%)	14 (4.1%)	0	14 (3.9%)
URINARY TRACT INFECTION	1 (1.5%)	6 (4.5%)	1 (0.7%)	8 (2.4%)	0	8 (2.3%)
SEPSIS	2 (2.9%)	2 (1.5%)	3 (2.2%)	7 (2.1%)	0	7 (2.0%)
LUNG INFECTION	0	2 (1.5%)	1 (0.7%)	3 (0.9%)	1 (6.3%)	4 (1.1%)
DEVICE RELATED INFECTION	0	0	1 (0.7%)	1 (0.3%)	1 (6.3%)	2 (0.6%)
METABOLISM AND NUTRITION DISORDERS						
Total number of patients with at least one adverse event	10 (14.7%)	13 (9.7%)	19 (13.9%)	42 (12.4%)	1 (6.3%)	43 (12.1%)
Total number of events	13	22	64	99	3	102
HYPOPHOSPHATAEMIA	3 (4.4%)	2 (1.5%)	4 (2.9%)	9 (2.7%)	1 (6.3%)	10 (2.8%)
HYPOKALAEMIA	0	3 (2.2%)	4 (2.9%)	7 (2.1%)	0	7 (2.0%)
HYPONATRAEMIA	1 (1.5%)	1 (0.7%)	5 (3.6%)	7 (2.1%)	0	7 (2.0%)
HYPERGLYCAEMIA	1 (1.5%)	1 (0.7%)	4 (2.9%)	6 (1.8%)	0	6 (1.7%)
HYPERURICAEMIA	2 (2.9%)	2 (1.5%)	2 (1.5%)	6 (1.8%)	0	6 (1.7%)
HYPOALBUMINAEMIA	1 (1.5%)	1 (0.7%)	3 (2.2%)	5 (1.5%)	0	5 (1.4%)
HYPOCALCAEMIA	1 (1.5%)	0	3 (2.2%)	4 (1.2%)	0	4 (1.1%)
DECREASED APPETITE	0	0	0	0	1 (6.3%)	1 (0.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Total number of patients with at least one adverse event	11 (16.2%)	6 (4.5%)	13 (9.5%)	30 (8.8%)	0	30 (8.5%)
Total number of events	12	8	17	37	0	37
FATIGUE	8 (11.8%)	2 (1.5%)	5 (3.6%)	15 (4.4%)	0	15 (4.2%)
ASTHENIA	0	0	4 (2.9%)	4 (1.2%)	0	4 (1.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
Total number of patients with at least one adverse event	6 (8.8%)	7 (5.2%)	7 (5.1%)	20 (5.9%)	1 (6.3%)	21 (5.9%)
Total number of events	6	14	7	27	1	28
BACK PAIN	0	2 (1.5%)	3 (2.2%)	5 (1.5%)	0	5 (1.4%)
MYALGIA	0	3 (2.2%)	0	3 (0.9%)	0	3 (0.8%)
PAIN IN EXTREMITY	0	0	0	0	1 (6.3%)	1 (0.3%)
GASTROINTESTINAL DISORDERS						
Total number of patients with at least one adverse event	2 (2.9%)	8 (6.0%)	7 (5.1%)	17 (5.0%)	2 (12.5%)	19 (5.4%)
Total number of events	2	13	11	26	4	30
DIARRHOEA	1 (1.5%)	4 (3.0%)	2 (1.5%)	7 (2.1%)	0	7 (2.0%)
ABDOMINAL PAIN	0	1 (0.7%)	0	1 (0.3%)	1 (6.3%)	2 (0.6%)
CONSTIPATION	0	0	1 (0.7%)	1 (0.3%)	1 (6.3%)	2 (0.6%)
DYSPHAGIA	0	0	0	0	1 (6.3%)	1 (0.3%)
OESOPHAGEAL STENOSIS	0	0	0	0	1 (6.3%)	1 (0.3%)
VASCULAR DISORDERS						
Total number of patients with at least one adverse event	4 (5.9%)	11 (8.2%)	3 (2.2%)	18 (5.3%)	0	18 (5.1%)
Total number of events	5	13	10	28	0	28
HYPOTENSION	2 (2.9%)	3 (2.2%)	2 (1.5%)	7 (2.1%)	0	7 (2.0%)
HYPERTENSION	1 (1.5%)	3 (2.2%)	1 (0.7%)	5 (1.5%)	0	5 (1.4%)
CARDIAC DISORDERS						
Total number of patients with at least one adverse event	6 (8.8%)	5 (3.7%)	2 (1.5%)	13 (3.8%)	1 (6.3%)	14 (3.9%)
Total number of events	7	7	2	16	1	17
PERICARDIAL EFFUSION	1 (1.5%)	2 (1.5%)	0	3 (0.9%)	1 (6.3%)	4 (1.1%)
CARDIO-RESPIRATORY ARREST	2 (2.9%)	0	0	2 (0.6%)	0	2 (0.6%)
PSYCHIATRIC DISORDERS						
Total number of patients with at least one adverse event	3 (4.4%)	4 (3.0%)	6 (4.4%)	13 (3.8%)	0	13 (3.7%)
Total number of events	3	5	7	15	0	15
INJURY POISONING AND PROCEDURAL COMPLICATIONS						
Total number of patients with at least one adverse event	2 (2.9%)	4 (3.0%)	6 (4.4%)	12 (3.5%)	1 (6.3%)	13 (3.7%)
Total number of events	2	4	7	13	1	14
FEMUR FRACTURE	0	0	0	0	1 (6.3%)	1 (0.3%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Total number of patients with at least one adverse event	0	5 (3.7%)	1 (0.7%)	6 (1.8%)	0	6 (1.7%)
Total number of events	0	5	1	6	0	6
RASH	0	3 (2.2%)	0	3 (0.9%)	0	3 (0.8%)
RENAL AND URINARY DISORDERS						
Total number of patients with at least one adverse event	0	1 (0.7%)	4 (2.9%)	5 (1.5%)	0	5 (1.4%)
Total number of events	0	1	9	10	0	10
ACUTE KIDNEY INJURY	0	0	3 (2.2%)	3 (0.9%)	0	3 (0.8%)
HEPATOBILIARY DISORDERS						
Total number of patients with at least one adverse event	0	0	3 (2.2%)	3 (0.9%)	0	3 (0.8%)
Total number of events	0	0	3	3	0	3

Investigator text for AEs encoded using MedDRA version 21.0.
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 coun
frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Adverse Events appear in this table if the incidence in any Study Basket is >= 2%.

Treatment-related AEs

The causality relationship of study drug to an AE was assessed by the Investigator. An AE is reported as related to entrectinib if the investigator assessed it as possibly, probably, or definitely related.

Most (91.5%) patients in the overall integrated safety population had at least one AE that was considered by the investigator to be related to entrectinib treatment. The most frequently reported (≥10% of patients) treatment-related AEs by PT were dysgeusia (41.4%), fatigue (27.9%), dizziness (25.4%), constipation (23.7%), diarrhoea (22.8%), nausea (20.8%), weight increased (19.4%), paraesthesia (18.9%), blood creatinine increased (15.2%), myalgia (15.2%), oedema peripheral (14.1%), vomiting (13.5%), arthralgia (12.4%), anaemia (12.1%), and AST increased (11.0%).

Adverse drug reactions

Adverse drug reactions (ADRs) were selected based on Sponsor causality assessment and a frequency of ≥10% for individual preferred terms or group of preferred terms 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. The ADR frequencies shown in Table below are based on the expanded integrated safety population of N=504 patients.

Table 77: Summary of adverse drug reactions in patients treated with entrectinib in clinical trials

System Organ Class	Adverse Reaction	Entrectinib N=504		
		All grades (%)	Frequency category (all grades)	Grade 3-5 (%)
Infections and infestations	Lung Infection[1]	13.1	very common	6.0[19]
	Urinary tract infection	12.7	very common	2.6
Blood and lymphatic system disorders	Anaemia	28.2	very common	9.7
	Neutropenia[2]	11.3	very common	4.4
Metabolism and nutritional disorders	Hyperuricaemia	9.1	common	1.8
	Weight increased	26.4	very common	7.3
	Decreased appetite	11.9	very common	0.2
	Dehydration	7.9	common	1.0
	Tumor lysis syndrome	0.2	uncommon	0.2[19]
Nervous system disorders	Dysgeusia	42.3	very common	0.4
	Dizziness[3]	39.7	very common	1.2
	Dysaesthesia[4]	29.0	very common	0.2
	Cognitive disorders	24.2	very common	4.4
	Headache	17.5	very common	1.0
	Peripheral Sensory Neuropathy[5]	15.7	very common	1.0
	Ataxia[7]	15.7	very common	0.8
	Sleep disturbances[16]	13.5	very common	0.4
	Mood disorders	9.1	common	0.6
	Syncope	4.6	common	3.0
Eye disorders	Vision Blurred[8]	11.9	very common	0.4
Cardiac disorders	Congestive Heart Failure[9]	3.0	common	2.2
	Electrocardiogram QTc prolonged	2.0	common	0.6
Vascular disorders	Hypotension[10]	16.5	very common	2.4
Respiratory, thoracic and mediastinal disorders	Dyspnoea	27.0	very common	5.8[19]
	Cough	21.4	very common	0.6
	Pleural effusion	6.9	common	2.8
Gastrointestinal disorders	Constipation	42.9	very common	0.4
	Diarrhoea	33.5	very common	2.6
	Nausea	32.1	very common	0.8
	Vomiting	23.2	very common	1.2
	Abdominal pain	11.1	very common	0.6
	Dysphagia	10.1	very common	0.4
Hepatobiliary disorders	AST increased	17.5	very common	3.6
	ALT increased	16.1	very common	3.4
Skin and subcutaneous tissue disorders	Rash[11]	11.5	very common	1.4
Musculoskeletal and connective tissue disorders	Myalgia	19.6	very common	0.6
	Arthralgia	19.0	very common	0.6
	Muscular weakness	12.3	very common	1.2
	Fractures[12]	6.2	common	2.4
Renal and urinary disorders	Blood creatinine increased	25.4	very common	0.6
	Urinary retention[17]	10.9	very common	0.6
General disorders and administration site conditions	Fatigue[13]	45.0	very common	5.0
	Oedema[14]	37.3	very common	1.4
	Pain[15]	24.4	very common	1.6
	Pyrexia	20.0	very common	0.8

[1] Lung infection includes the PTs bronchitis, lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection, upper respiratory tract infection.

[2] Neutropenia includes the PTs neutropenia, neutrophil count decreased.

[3] Dizziness includes the PTs dizziness, vertigo, dizziness postural.

[4] Dysaesthesia includes the PTs paraesthesia, hyperaesthesia, hypoaesthesia, dysaesthesia.

[5] Cognitive impairment includes the PTs cognitive disorder, confusional state, disturbance in attention, memory impairment, amnesia, mental status changes, hallucination, delirium, 'hallucination visual' and mental disorder.

[6] Peripheral sensory neuropathy includes the PTs neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy.

[7] Ataxia includes the PTs ataxia, balance disorder, gait disturbances.

[8] Vision blurred includes the PTs diplopia, vision blurred, visual impairment.

[9] Congestive heart failure includes the PTs acute right ventricular failure, cardiac failure, cardiac failure congestive, chronic right ventricular failure, ejection fraction decreased,pulmonary oedema.

[10] Hypotension includes the PTs hypotension, orthostatic hypotension.

[11] Rash includes the PTs rash, rash maculopapular, rash pruritic, rash erythematous, rash popular.

[12] Fractures includes the PTs humerus fracture, foot fracture, ankle fracture, femoral neck fracture, stress fracture, fibula fracture, fracture, rib fracture, spinal fracture, wrist fracture, femur fracture, pathological fracture.

[13] Fatigue includes the PTs fatigue, asthenia.

[14] Oedema includes the PTs face oedema, fluid retention, generalized oedema, localized oedema, oedema, oedema peripheral, peripheral swelling.

[15] Pain includes the PTs back pain, neck pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity.

[16] Sleep disturbances includes the PTs hypersomnia, insomnia, sleep disorder, somnolence.

[17] Urinary retention includes the PTs urinary retention, urinary incontinence, urinary hesitation, micturition disorder, micturition urgency.

[18] Mood disorders includes the PTs anxiety, affect lability, affective disorder, agitation, depressed mood, euphoric mood, mood altered, mood swings, irritability, depression, persistent depressive disorder, psychomotor retardation.

[19] Grade 5 (fatal) ADRs were reported for dyspnea (2 patients), pneumonia (2 patients) and tumor lysis syndrome (1 patient).

AEs of special interest

AEs of special interest were not pre-defined in the study protocols. Selected AEs were defined by the Applicant on the basis of previous clinical experience, mechanism of action and safety profile from drugs with similar targets. Selected AEs were defined using Standardized MedDRA queries (SMQs), where applicable. If no SMQs were available, MedDRA System Organ Class (SOC), High Level Term (HLT), High Level Group Term (HLGT), Roche Standard MedDRA Adverse Event Grouped Terms (AEGTs), or PT were used (see Table below).

Table 78: Selected Adverse Events Search Criteria

Selected AE		Search Criteria
Neurologic toxicity		Nervous system disorder (SOC) and Psychiatric Disorders (SOC)
(1)	Cognitive disorders	Entrectinib- cognitive impairment AEGT
(2)	Peripheral sensory neuropathy	PTs: neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy
(3)	Dysaethesias	PTs: paraesthesia, hyperaesthesia, hypoaesthesia, dysaethesia
(4)	Ataxia	PTs: ataxia, balance disorder, gait disturbances
(5)	Syncope	PT: syncope
(6)	Seizure	PT: seizure
Changes in Weight		PTs: weight increased, weight decreased
Congestive heart failures		Cardiac failure (SMQ)- narrow
Increased creatinine and other renal events		Renal and urinary disorders (SOC), Renal function analyses (HLT)
Eye disorders		Eye disorders (SOC)
QTc interval prolongation		Torsade de pointes/QT prolongation (SMQ) - narrow
Elevated liver laboratory tests and other liver abnormalities		Liver related investigations, signs and symptoms (SMQ), Hepatobiliary disorders (SOC)
Pneumonitis events		Interstitial lung disease (SMQ)- narrow
Hematologic events		Blood and Lymphatic system disorders (SOC); Hematologic investigations (HLGT)

AEGT- Roche Standard MedDRA Adverse Event Grouped Terms; HLGT=high level group term; HLT=high level term; PT=preferred term; SMQ=standard MedDRA query; SOC = System Organ Class.

Neurologic Toxicity

Consistent with entrectinib's CNS activity and the known association of TRK receptors' involvement in neuronal development and maintenance of the central and peripheral nervous system, neurologic AEs have been observed in patients treated with entrectinib. Neurologic toxicity was defined as any AE from either nervous system disorder SOC or psychiatric disorders SOC. Neurological AEs were reported in 88.7% of patients in the overall integrated safety population. Most patients experienced events that were of Grade 1 (45.4%) or Grade 2 (26.5%) in severity. The most frequently reported (≥10% of patients) AEs (all grade) by PT were dysgeusia (43.7%), dizziness (34.6%), paraesthesia (20.6%), headache (17.7%), and muscular weakness (12.1%).

Cognitive disorders AEs

Cognitive disorders AEs (all grade) were reported in 25.9% of patients (see table below).

Table 79: Overview of Cognitive Disorders Adverse Events (CCOD: 31 May 2018; Safety Population)

MedDRA Preferred Term	NCI-CTCAE Grade	NTRK- Adult (N= 68)	ROS1 NSCLC-Adult (N= 134)	Other Adult (N= 137)	Pediatric (N= 16)	Total (N= 355)
Cognitive disorder	All	3 (4.4%)	11 (8.2%)	14 (10.2%)	0	28 (7.9%)
	1	2 (2.9%)	5 (3.7%)	10 (7.3%)	0	17 (4.8%)
	2	0	4 (3.0%)	2 (1.5%)	0	6 (1.70%)

	3	1 (1.5%)	2 (1.5%)	2 (1.5%)	0	5 (1.40%)
Confusional state	All	7 (10.3%)	8 (6.0%)	11 (8.0%)	0	26 (7.3%)
	1	6 (8.8%)	4 (3.0%)	7 (5.1%)	0	17 (4.8%)
	2	0	3 (2.2%)	2 (1.5%)	0	5 (1.4%)
	3	1 (1.5%)	1 (0.7%)	2 (1.5%)	0	4 (1.1%)
Disturbance in attention	All	4 (5.9%)	6 (4.5%)	6 (4.4%)	1 (6.3%)	17 (4.8%)
	1	4 (5.9%)	6 (4.5%)	5 (3.6%)	1 (6.3%)	16 (4.5%)
	3	0	0	1 (0.7%)	0	1 (0.3%)
Memory impairment	All	3 (4.4%)	9 (6.7%)	1 (0.7%)	0	13 (3.7%)
	1	2 (2.9%)	8 (6.0%)	1 (0.7%)	0	11 (3.1%)
	2	1 (1.5%)	1 (0.7%)	0	0	2 (0.6%)
Amnesia	All	1 (1.5%)	5 (3.7%)	3 (2.2%)	0	9 (2.5%)
	1	1 (1.5%)	5 (3.7%)	3 (2.2%)	0	9 (2.5%)
Mental status changes	All	2 (2.9%)	2 (1.5%)	2 (1.5%)	0	6 (1.7%)
	1	1 (1.5%)	0	0	0	1 (0.3%)
	3	1 (1.5%)	2 (1.5%)	2 (1.5%)	0	5 (1.4%)
Mental disorder	All	0	1 (0.7%)	0	0	1 (0.3%)
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	1 (0.7%)	0	0	1 (0.3%)
Hallucination	All	0	2 (1.5%)	2 (1.5%)	0	4 (1.1%)
	1	0	2 (1.5%)	1 (0.7%)	0	3 (0.8%)
	2	0	0	1 (0.7%)	0	1 (0.3%)
Delirium	All	0	1 (0.7%)	2 (1.5%)	0	3 (0.8%)
	1	0	0	2 (1.5%)	0	2 (0.6%)
	3	0	1 (0.7%)	0	0	1 (0.3%)
Hallucination, visual	All	1 (1.5%)	0	0	0	1 (0.3%)
	1	1 (1.5%)	0	0	0	1 (0.3%)

Note: Entrectinib- cognitive impairment AEGT were utilized to capture potential events of interest of cognitive disorders AE. Entrectinib- cognitive impairment AEGT include the PTs of altered state of consciousness, amnesia, amnestic disorder, cognitive disorder, confusional state, delirium, disorientation, disturbance in attention, hallucination, hallucination auditory, hallucination visual, hallucinations mixed, impaired reasoning, incoherent, judgement impaired, memory impairment, mental disorder, mental impairment, mental status changes.

In the updated safety population (CCOD: 31 October 2018), AEs were reported in 24.2% of patients; these included events reported as cognitive disorders (6.3%), confusional state (7.3%), disturbance in attention (3.8%), memory impairment (4.2%), amnesia (2.8%), mental status changes (1.2%), hallucination (1.0%), delirium (0.8%), visual hallucination (0.4%) and mental disorder (0.2%). Grade 3 cognitve disorders were reported in 4.4% of patients. Adult patients who had CNS disease at baseline had a higher frequency of these adverse reactions (29.7%) compared to those without CNS disease (23.1%). The median time to onset for cognitive disorders was 0.92 months.

Peripheral sensory neuropathy

Peripheral sensory neuropathy AEs (all grade) were reported in 17.7% of patients (see Table below).

Table 80: Overview of Peripheral Sensory Neuropathy Adverse Events (CCOD: 31 May 2018; Safety population)

MedDRA Preferred Term	**NCI-CTCAE Grade**	**NTRK- Adult (N= 68)**	**ROS1 NSCLC-Adult (N= 134)**	**Other Adult (N= 137)**	**Paediatric (N= 16)**	**Total (N= 355)**
Neuropathy peripheral	All	6 (8.8%)	17 (12.7%)	8(5.8%)	0	31(8.7%)
	1	4 (5.9%)	14 (10.4%)	7 (5.1%)	0	25(7.0%)
	2	2 (2.9%)	3 (2.2%)	1(0.7%)	0	6(1.7%)
Peripheral sensory neuropathy	All	7 (10.3%)	10 (7.5%)	11 (8.0%)	1 (6.3%)	29 (8.2%)
	1	3 (4.4%)	5 (3.7%)	7 (5.1%)	1 (6.3%)	16 (4.5%)
	2	3 (4.4%)	4 (3.0%)	2 (1.5%)	0	9 (2.5%)

MedDRA Preferred Term	NCI-CTCAE Grade	NTRK- Adult (N= 68)	ROS1 NSCLC-Adult (N= 134)	Other Adult (N= 137)	Paediatric (N= 16)	Total (N= 355)
	3	1 (1.5%)	1 (0.7%)	2 (1.5%)	0	4 (1.1%)
Peripheral	All	1 (1.5%)	1 (0.7%)	2 (1.5%)	1 (6.3%)	5 (1.4%)
motor	1	1 (1.5%)	0	1 (0.7%)	1 (6.3%)	3 (0.8%)
neuropathy	2	0	1 (0.7%)	1 (0.7%)	0	2 (0.6%)
Neuralgia	All	0	2 (1.5%)	0	0	2 (0.6%)
	1	0	2 (1.5%)	0	0	2 (0.6%)

In the updated safety population (CCOD: 31 October 2018), peripheral sensory neuropathy was reported in 15.7% of patients. The median time to onset was 0.49 months (range 0.03 months to 20.93 months) and the median duration was 0.8 months (range: 0.07 months to 6.01 months). The majority of patients (55.7%) recovered from peripheral neuropathy.

Dysaesthesias

Table 81: Overview of Dysaesthesias Adverse Events (**CCOD: 31 May 2018;** Safety population)

MedDRA Preferred Term	NCI-CTCAE Grade	NTRK- Adult (N= 68)	ROS1 NSCLC-Adult (N= 134)	Other Adult (N= 137)	Pediatric (N= 16)	Total (N= 355)
Paraesthesia	All	14 (20.6%)	24 (17.9%)	33 (24.1%)	2 (12.5%)	73 (20.6%)
	1	11 (16.2%)	17 (12.7%)	33 (24.1%)	2 (12.5%)	63 (17.7%)
	2	3 (4.4%)	7 (5.2%)	0	0	10 (2.8%)
Hyperaesthesia	All	2 (2.9%)	13 (9.7%)	9 (6.6%)	0	24 (6.8%)
	1	2 (2.9%)	12 (9.0%)	9 (6.6%)	0	23 (6.5%)
	3	0	1 (0.7%)	0	0	1 (0.3%)
Hypoaesthesia	All	1 (1.5%)	10 (7.5%)	4 (2.9%)	0	15 (4.2%)
	1	1 (1.5%)	8 (6.0%)	3 (2.2%)	0	12 (3.4%)
	2	0	2 (1.5%)	1 (0.7%)	0	3 (0.8%)
Dysaesthesia	All	0	2 (1.5%)	1 (0.7%)	1 (6.3%)	4 (1.1%)
	1	0	2 (1.5%)	1 (0.7%)	1 (6.3%)	4 (1.1%)

In the updated safety population (CCOD: 31 October 2018), the overall frequency of dysesthesias AEs (PTs of paraesthesia, hyperaesthesia, hypoaesthesia, dysaethesia; all grade) reported was 29.0% in the expanded integrated safety population. Most dysesthesias AEs were of Grade 1 or Grade 2, and no Grade 4 dysesthesias AEs were reported in the overall integrated safety population.

Ataxia

Table 82: Overview of Ataxia Adverse Events (CCOD: 31 May 2018; Safety population)

MedDRA Preferred Term	NCI-CTCAE Grade	NTRK-Adult (N= 68)	ROS1 NSCLC-Adult (N= 134)	Other Adult (N= 137)	Pediatric (N= 16)	Total (N= 355)
Ataxia	All	4 (5.9%)	7 (5.2%)	5 (3.6%)	1 (6.3%)	17 (4.8%)
	1	3 (4.4%)	3 (2.2%)	3 (2.2%)	0	9 (2.5%)
	2	1 (1.5%)	3 (2.2%)	0	1 (6.3%)	5 (1.4%)
	3	0	1 (0.7%)	2 (1.5%)	0	3 (0.8%)
Balance	All	3 (4.4%)	11 (8.0%)	11 (8.2%)	0	25 (7.0%)
disorder	1	2 (2.9%)	11 (8.2%)	9 (6.6%)	0	22 (6.2%)
	2	1 (1.5%)	0	2 (1.5%)	0	3 (0.8%)
Gait	All	5 (7.4%)	7 (5.2%)	11 (8.0%)	1 (6.3%)	24 (6.8%)
disturbance	1	4 (5.9%)	5 (3.7%)	7 (5.1%)	1 (6.3%)	17 (4.8%)
	2	1 (1.5%)	2 (1.5%)	4 (2.9%)	0	7 (2.0%)

In the updated safety population (CCOD: 31 October 2018), AEs (PTs ataxia, balance disorder, gait disturbances; all grade) were reported in 15.7% of patients. The median time to onset for ataxia was

0.4 months (range: 0.03 months to 28.19 months) and the median duration was 0.7 months (range: 0.03 months to 11.99 months). The majority of patients (67.1%) recovered from ataxia. Ataxia related adverse reactions were observed more frequently in elderly patients (23.8%) compared to patients below 65 years of age (12.8%).

Syncope

Table 83: Overview of Syncope (CCOD: 31 May 2018; Safety population)

MedDRA Preferred Term	NCI-CTCAE Grade	NTRK- Adult (N= 68)	ROS1 NSCLC-Adult (N= 134)	Other Adult (N= 137)	Pediatric (N= 16)	Total (N= 355)
Syncope	All	4 (5.9%)	5 (3.7%)	4	1 (6.3%)	14 (3.9%)
	1	0	1 (0.7%)	3 (2.2%)	0	4 (1.1%)
	2	1 (1.5%)	0	0	0	1 (0.3%)
	3	3 (4.4%)	4 (3.0%)	1 (0.7%)	1 (6.3%)	9 (2.5%)

In the updated safety population (CCOD: 31 October 2018), syncope (by PT; all grade) was reported in 4.6% of patients. All Grade 3 events (3.0%) had resolved by the time of the CCOD. Overall, the nature and severity of syncope events reported are consistent with those reported in the previous analyses.

Seizure

In the updated safety population (CCOD: 31 October 2018), AEs of seizure (by PT) were reported in 2.2% of patients, all Grade 1 or 2 including one 3 –year old paediatric patient. All patients experiencing seizures had either brain metastases or primary brain tumour at baseline

Increased Creatinine and Other Renal Events

In the updated safety population (CCOD: 31 October 2018), increased creatinine and other renal events (Renal and urinary disorders [SOC], Renal function analyses [HLT]; all grade) were reported in 40.5% of patients. Consistent to renal events analysed in previous reports, the most frequently reported event was blood creatinine increased (25.4%). Most blood creatinine increased events observed continue to be Grade 1 or 2. No new event of Grade 3 blood creatinine increased has been reported, and no clinically significant sequelae were reported in patients who experienced blood creatinine increased. There were no Grade 4 events reported. Acute kidney injury was reported in 3.6% of patients, with most events being of Grade 1 or 2 in severity. Grade 3 acute kidney injury was reported in 5 patients (1.0%) with 2 of these cases (0.6%) being serious. Each of the Grade 3 events of acute kidney injury resolved.

Hematologic Toxicity

In the updated safety population (CCOD: 31 October 2018), hematologic AEs (Blood and Lymphatic system disorders [SOC], Hematologic investigations [HLGT]; all grades) were reported in 37.1% of patients. The most frequently reported hematologic toxicities were anemia (all grade: 28.2%, Grade 3: 9.7%) and neutropenia AEs (PTs of neutrophil count decreased and neutropenia) (all grade: 11.3%, Grade 3 or 4: 4.4%). Anemia and neutropenia AEs (all grade and Grade 3 or 4) were reported more frequently in the paediatric population compared to the adult population. Based on laboratory data, the majority of patients who experienced post-baseline shifts in hematology parameters had shifts from baseline grade to Grade 1 or 2. Few patients had clinically relevant treatment-emergent worsening of laboratory parameters (defined as change from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline) with the most common (≥2% of patients) being worsening to Grade 3 or 4 low lymphocytes levels (10.7%), followed by low hemoglobin (9.2%) and low neutrophils (6.3%). The laboratory value changes were transient and returned to baseline.

Eye Disorders

Eye disorders reported across clinical trials included vision blurred (8.5%), diplopia (2.6%), and visual impairment (1.6%). The median time to onset for eye disorders was 1.9 months (range: 0.03 months to 21.59 months). The median duration of eye disorders was 1 month (range 0.03 months to 14.49 months). The majority of patients (61.7%) recovered from the eye disorder adverse reactions.

Elevated Liver Laboratory Tests and Other Liver Abnormalities

In the updated safety population (CCOD: 31 October 2018), abnormal liver function test and liver dysfunction AEs (Liver related investigations, signs and symptoms [SMQ], Hepatobiliary disorders [SOC]; all grade) were reported in 22.6% of patients, similar to the frequency reported previously. Consistently, the most frequently reported events were laboratory abnormalities including AST increased (17.5%) and ALT increased (16.1%). The majority of liver abnormality events were Grade 1 and Grade 2 which resolved with no intervention. Overall, a larger proportion of paediatric patients experienced elevated transaminases compared to adult patients. No AE of "drug induced liver injury" was reported in any patient treated with entrectinib. As previously reported, five patients fulfilled the laboratory criteria of elevated ALT or AST (≥3 x ULN) in combination with elevated total bilirubin (≥2 x ULN). No additional patient in the expanded safety population satisfied these specific criteria. In each case, the observed liver abnormalities were indicative of baseline liver metastases or other causes and not drug induced liver injury.

Changes in Weight

In the updated safety population (CCOD: 31 October 2018), AE of weight increased (by PT) was reported in 26.4% of patients, similar to the frequency reported previously; the majority of which were assessed as related to entrectinib (20.6% of patients). Consistent with the findings noted previously, the majority of patients who had weight increase reported had Grade 1 or Grade 2 events. Grade 3 weight increased was reported in 7.9% of patients. Weight increase was reported as an adverse event in a higher proportion of pediatric patients than adult patients (all grade: 44.8% vs 25.3%, respectively; Grade 3: 13.8% vs. 6.9%). Most patients (21 of 25 patients) with Grade 3 weight increased were able to continue entrectinib with no dose adjustments. No AEs indicative of metabolic syndrome was concurrently reported in patients with weight increase. Adverse events of weight decreased (by PT) was reported in 2.6% of patients, mostly Grade 1 or 2.

Based on available data from patients in the overall expanded integrated safety population with non-missing baseline and at least one post-baseline weight measurement, 70.8% (342/483) of patients experienced Grade 1 or greater (≥5%) increase in body weight. Grade 3 (≥20% increase) post-baseline weight increase was measured in 19.9% (96/483) of patients. A higher proportion of pediatric patients experienced Grade 3 weight increases (41.4%) compared to adult patients (18.5%). A few patients (8.7%; 42/483) experienced Grade 1 or greater weight decrease.

Based on available BMI data, 184 patients in the expanded overall safety population experienced post-baseline shifts to a higher BMI category. Of a total of 243 patients who were of normal BMI at baseline, 101 patients shifted to overweight or obese categories post-baseline (n=95 and n=6, respectively). Of 55 patients who were underweight (≤18.5 kg/m2) at baseline, 27 patients shifted to normal or overweight categories (n=25 and n=2, respectively) post-baseline.

Congestive Heart Failure

Congestive heart failure events were reported in 3.4% of patients. An overview of congestive heart failure AEs by PT is provided in the table below.

Table 84: Overview of Congestive Heart Failure Adverse Events (CCOD: 31 May 2018; Safety population)

MedDRA Preferred Term	NCI-CTCAE Grade	NTRK- Adult (N= 68)	ROS1 NSCLC-Adult (N= 134)	Other Adult (N= 137)	Pediatric (N= 16)	Total (N= 355)
Ejection fraction decreased	All	0	1(0.7%)	2(1.5%)	1 (6.3%)	4 (1.1%)
	2	0	0	1(0.7%)	1(6.3%)	2 (0.6%)
	3	0	1(0.7%)	1(0.7%)	0	2 (0.6%)
Pulmonary oedema	All	0	0	3 (2.2%)	1 (6.3%)	4 (1.1%)
	1	0	0	1 (0.7%)	0	1 (0.3%)
	3	0	0	2 (1.5%)	1 (6.3%)	3 (0.8%)
Cardiac failure	All	1(1.5%)	2 (1.5%)	0	0	3 (0.8%)
	1	0	1 (0.7%)	0	0	1 (0.3%)
	3	1 (1.5%)	1 (0.75%)	0	0	2 (0.6%)
Cardiac failure congestive	All	1 (1.5%)	1 (0.7%)	1 (0.7%)	0	3 (0.8%)
	2	0	1 (0.7%)	1 (0.7%)	0	2 (0.6%)
	3	1 (1.5%)	0	0	0	1 (0.3%)
Acute right ventricular failure	All	1 (1.5%)	0	0	0	1 (0.3%)
	3	1 (1.5%)	0	0	0	1 (0.3%)
Cardiogenic shock [a]	All	0	1 (0.7%)	0	0	1 (0.3%)
Chronic right ventricular failure	All	1 (1.5%)	0	0	0	1 (0.3%)
	2	1 (1.5%)	0	0	0	1 (0.3%)

[a] The nature and clinical course of the Grade 5 cardiogenic shock fatal event was not consistent with congestive heart failure and was therefore excluded from the incidence of congestive heart failure AEs. The event of cardiogenic shock is included in table 18 for the purpose of transparency.

In the updated safety population (CCOD: 31 October 2018), congestive heart failure events (PTs under Cardiac failure [SMQ]-narrow) were reported in 3.2% of patients. Consistent with the previous analyses, most patients with congestive heart failure events experienced Grade 3 (2.0% of patients) events. Serious events were reported in 9 (1.8%) patients, and compared to the previous analyses, included one additional patient in the expanded safety evaluable population enrolled after 30 November 2017 with a serious Grade 3 event of cardiac failure requiring hospitalization and dose interruption. The event resolved and the patient could continue entrectinib treatment. A Grade 4 event of serious pulmonary edema was reported in a pediatric patient with infantile fibrosarcoma. Entrectinib was withdrawn and the event resolved. The event was considered related to entrectinib. Other events noted in this patient included dyspnea, hypoxia, lower respiratory tract infection, upper respiratory tract, pneumonia, respiratory acidosis and respiratory failure. One Grade 5 cardiogenic shock was reported in a patient with NSCLC due to pericardial effusion and pericardial tamponade. The nature and clinical course of the Grade 5 cardiogenic shock fatal event was not consistent with congestive heart failure. No other Grade 5 congestive heart failure event has been reported.

Pneumonitis

In the updated safety population (CCOD: 31 October 2018), pneumonitis events were experienced by 2.0% of patients and included pneumonitis and radiation pneumonitis (0.8% each), alveolitis (0.4%), and interstitial lung disease (0.2%). The large majority of events were Grade 1 and 2. Grade 3 pneumonitis events, all serious, were reported in 4 patients in the expanded safety population,

including an additional event of Grade 3 radiation pneumonitis in one patient and Grade 3 alveolitis in one other patient enrolled after 30 November 2017.

QT Interval Prolongation

Among the 504 patients who received entrectinib across clinical trials, 17 (4.0%) patients with at least one post-baseline ECG assessment experienced QTcF interval prolongation of >60 ms after starting entrectinib, and 12 (2.8%) patients had a QTcF interval of ≥500 ms (see sections 4.4 and 4.8 of the SmPC).

Fractures

In the updated safety population (CCOD: 31 October 2018), fractures were reported in 6.2% (31/504) of patients in the expanded safety population and were more frequently observed in paediatric patients aged <18 years (20.7%) than adult patients (5.3%). In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area, while in paediatric patients all fractures occurred in patients with minimal or no trauma. The incidence of all fractures by preferred term was <1%. In both adult and paediatric patients, most were hip or other lower extremity fractures. The most frequent fractures by preferred term (>0.5%, i.e., 3 or more patients) were humerus fracture and pathological fracture (4 patients each), ankle fracture, foot fracture and tibia fracture (3 patients each). Grade 3 fractures were reported in 2.4% (12/504) of patients, with pathological fracture and femoral neck fracture being the only Grade 3 events by preferred term reported in more than one patient. There were no fractures Grade ≥4. The median time to onset of the first fracture in patients who experienced fractures was 3.4 months (range: 0.3 to 18.5 months). None of the fracture events led to discontinuation of entrectinib. In the majority of cases no action with study drug was taken for fractures; in other cases entrectinib was interrupted, and the patient continued to receive entrectinib. At the time of the CCOD, the majority of fractures had resolved.

Serious adverse event/deaths/other significant events

SAEs

In the overall integrated safety population, 137 (38.6%) patients experienced at least one SAE. Treatment-related SAEs were reported in 30 (8.5%) patients.

Table 85: Serious adverse events related to study treatment (CCOD: 31 May 2018; Safety population)

Protocols: GO40782, GO40783, GO40784, CO40778
Enrollment cutoff: Nov 30 2017, CCOD: May 31 2018, DBL: Jul 31 2018

MedDRA System Organ Class MedDRA Preferred Term	NTRK-Adult (N=68)	ROS1 NSCLC-Adult (N=134)	Other-Adult (N=137)	Total-Adult (N=339)	Pediatric (N=16)	Total (N=355)
Total number of patients with at least one adverse event	7 (10.3%)	15 (11.2%)	7 (5.1%)	29 (8.6%)	1 (6.3%)	30 (8.5%)
Overall total number of events	10	21	10	41	4	45
NERVOUS SYSTEM DISORDERS						
Total number of patients with at least one adverse event	3 (4.4%)	4 (3.0%)	3 (2.2%)	10 (2.9%)	0	10 (2.8%)
Total number of events	3	5	3	11	0	11
COGNITIVE DISORDER	1 (1.5%)	1 (0.7%)	2 (1.5%)	4 (1.2%)	0	4 (1.1%)
ATAXIA	0	1 (0.7%)	1 (0.7%)	2 (0.6%)	0	2 (0.6%)
CEREBELLAR ATAXIA	1 (1.5%)	0	0	1 (0.3%)	0	1 (0.3%)
DIZZINESS	1 (1.5%)	0	0	1 (0.3%)	0	1 (0.3%)
DYSARTHRIA	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
LIMBIC ENCEPHALITIS	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
CARDIAC DISORDERS						
Total number of patients with at least one adverse event	1 (1.5%)	3 (2.2%)	0	4 (1.2%)	0	4 (1.1%)
Total number of events	1	4	0	5	0	5
CARDIAC FAILURE	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
CARDIAC FAILURE CONGESTIVE	1 (1.5%)	0	0	1 (0.3%)	0	1 (0.3%)
MYOCARDITIS	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
SINUS ARRHYTHMIA	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
VENTRICULAR EXTRASYSTOLES	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Total number of patients with at least one adverse event	1 (1.5%)	2 (1.5%)	1 (0.7%)	4 (1.2%)	0	4 (1.1%)
Total number of events	1	3	1	5	0	5
PYREXIA	0	2 (1.5%)	0	2 (0.6%)	0	2 (0.6%)
FATIGUE	0	0	1 (0.7%)	1 (0.3%)	0	1 (0.3%)
OEDEMA PERIPHERAL	1 (1.5%)	0	0	1 (0.3%)	0	1 (0.3%)
VASCULAR DISORDERS						
Total number of patients with at least one adverse event	1 (1.5%)	2 (1.5%)	0	3 (0.9%)	0	3 (0.8%)
Total number of events	1	2	0	3	0	3
HYPOTENSION	1 (1.5%)	1 (0.7%)	0	2 (0.6%)	0	2 (0.6%)
ORTHOSTATIC HYPOTENSION	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
RESPIRATORY THORACIC AND MEDIASTINAL DISORDERS						
Total number of patients with at least one adverse event	1 (1.5%)	0	1 (0.7%)	2 (0.6%)	1 (6.3%)	3 (0.8%)
Total number of events	1	0	1	2	4	6
PULMONARY OEDEMA	0	0	1 (0.7%)	1 (0.3%)	1 (6.3%)	2 (0.6%)
DYSPNOEA	1 (1.5%)	0	0	1 (0.3%)	0	1 (0.3%)
EYE DISORDERS						
Total number of patients with at least one adverse event	1 (1.5%)	0	1 (0.7%)	2 (0.6%)	0	2 (0.6%)
Total number of events	1	0	1	2	0	2
DIPLOPIA	1 (1.5%)	0	0	1 (0.3%)	0	1 (0.3%)
VISION BLURRED	0	0	1 (0.7%)	1 (0.3%)	0	1 (0.3%)
GASTROINTESTINAL DISORDERS						
Total number of patients with at least one adverse event	0	1 (0.7%)	1 (0.7%)	2 (0.6%)	0	2 (0.6%)
Total number of events	0	2	1	3	0	3
ANORECTAL DISORDER	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
DIARRHOEA	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
DYSPHAGIA	0	0	1 (0.7%)	1 (0.3%)	0	1 (0.3%)
INVESTIGATIONS						
Total number of patients with at least one adverse event	1 (1.5%)	1 (0.7%)	0	2 (0.6%)	0	2 (0.6%)
Total number of events	1	2	0	3	0	3
BLOOD CREATININE INCREASED	1 (1.5%)	1 (0.7%)	0	2 (0.6%)	0	2 (0.6%)
METABOLISM AND NUTRITION DISORDERS						
Total number of patients with at least one adverse event	0	1 (0.7%)	1 (0.7%)	2 (0.6%)	0	2 (0.6%)
Total number of events	0	1	1	2	0	2
DEHYDRATION	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
HYPONATRAEMIA	0	0	1 (0.7%)	1 (0.3%)	0	1 (0.3%)
PSYCHIATRIC DISORDERS						
Total number of patients with at least one adverse event	0	1 (0.7%)	1 (0.7%)	2 (0.6%)	0	2 (0.6%)
Total number of events	0	1	1	2	0	2
MENTAL STATUS CHANGES	0	1 (0.7%)	1 (0.7%)	2 (0.6%)	0	2 (0.6%)
ENDOCRINE DISORDERS						
Total number of patients with at least one adverse event	1 (1.5%)	0	0	1 (0.3%)	0	1 (0.3%)
Total number of events	1	0	0	1	0	1
HYPOGONADISM	1 (1.5%)	0	0	1 (0.3%)	0	1 (0.3%)
INJURY POISONING AND PROCEDURAL COMPLICATIONS						
Total number of patients with at least one adverse event	0	0	1 (0.7%)	1 (0.3%)	0	1 (0.3%)
Total number of events	0	0	1	1	0	1
FALL	0	0	1 (0.7%)	1 (0.3%)	0	1 (0.3%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Total number of patients with at least one adverse event	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
Total number of events	0	1	0	1	0	1
RASH	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 21.0.
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. frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

In the updated safety population (CCOD: 31 October 2018), In the overall integrated safety population, 201 (39.9%) patients experienced at least one SAE. Treatment- related SAEs were reported in 49 (9.7%) patients, with the most frequently reported being cognitive disorders (1.0%). The most frequently reported SAEs regardless of causality by SOC (≥ 5% of patients, any grade) were as follows:

- respiratory thoracic and mediastinal disorders (11.9%), the most frequently reported (≥2% of patients) PTs including dyspnea (4.6%), pleural effusion (3.0%), and pulmonary embolism (2.0%). No new additional respiratory SAEs were reported in ≥ 2% of patients in the expanded safety population.

- infections and infestations (11.1%), the most frequently reported PT being pneumonia (4.0%). Other respiratory infections included upper respiratory tract infection (0.6%), lung infection (1.4%), lower respiratory tract infection (0.4%).

- nervous system disorders (8.5%), the most frequently reported PTs being cognitive disorder and syncope (1.4% each). Other SAEs from this SOC were seizure (0.8%), hydrocephalus and headache (0.6% each), ataxia, cerebrovascular accident and dizziness (0.4% each).

Compared to the earlier safety analyses, the overall incidence of SAEs in pediatric patients in this updated analysis in the expanded integrated population is higher, and the magnitude in the difference in incidence of SAEs between adult and pediatric patients that was evident in the earlier analyses, was less marked (<18 years: 34.5% vs. ≥18 years old: 40.2%).

Deaths

Grade 5 AEs occurred in 20 (5.6%) patients; none of which were assessed by the investigator as related to entrectinib. All Grade 5 events occurred in the adult population. A summary of fatal AEs by PT is provided in Table below.

Table 86: Adverse Events Resulting in Death

Adverse Events Resulting in Death, Safety-Evaluable Patients
Protocols: GO40782, GO40783, GO40784, CO40778
Enrollment cutoff: Nov 30 2017, CCOD: May 31 2018, DBL: Jul 31 2018

MedDRA Preferred Term	NTRK-Adult (N=68)	ROS1 NSCLC-Adult (N=134)	Other-Adult (N=137)	Total-Adult (N=339)	Pediatric (N=16)	Total (N=355)
Total number of deaths	6 (8.8%)	9 (6.7%)	5 (3.6%)	20 (5.9%)	0	20 (5.6%)
ACUTE RESPIRATORY FAILURE	2 (2.9%)	0	0	2 (0.6%)	0	2 (0.6%)
CARDIO-RESPIRATORY ARREST	2 (2.9%)	0	0	2 (0.6%)	0	2 (0.6%)
DYSPNOEA	0	1 (0.7%)	1 (0.7%)	2 (0.6%)	0	2 (0.6%)
METASTASES TO MENINGES	0	2 (1.5%)	0	2 (0.6%)	0	2 (0.6%)
PNEUMONIA	1 (1.5%)	1 (0.7%)	0	2 (0.6%)	0	2 (0.6%)
SEPSIS	1 (1.5%)	1 (0.7%)	0	2 (0.6%)	0	2 (0.6%)
CARDIOGENIC SHOCK	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
CEREBRAL INFARCTION	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
COMPLETED SUICIDE	0	0	1 (0.7%)	1 (0.3%)	0	1 (0.3%)
LARGE INTESTINE PERFORATION	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
PULMONARY EMBOLISM	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.3%)
RESPIRATORY FAILURE	0	0	1 (0.7%)	1 (0.3%)	0	1 (0.3%)
SEPTIC SHOCK	0	0	1 (0.7%)	1 (0.3%)	0	1 (0.3%)
TUMOUR LYSIS SYNDROME	0	0	1 (0.7%)	1 (0.3%)	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 21.0.

Ten of the 20 Grade 5 AEs were respiratory AEs, the majority of which (9 of 10) were reported in patients with lung cancers or lung metastasis in the context of disease progression or deterioration of underlying cancers. Overall, there were no patterns with respect to the type of Grade 5 AEs reported, and the majority of Grade 5 AEs were reported in the context of worsening of underlying disease or complications of the underlying malignancy. No fatal AEs were reported in pediatric patients.

There were a total of 123 (24.4%) deaths in the overall integrated safety population (see Table below).

Table 87: Deaths by cause (CCOD: 31 October 2018; safety evaluable population)

Protocols: GO40782, GO40783, GO40784, CO40778
CCOD: Oct 31 2018, DBL: Dec 21 2018

Cause of Death	NTRK-Adult (N=113)	ROS1 NSCLC-Adult (N=210)	Other-Adult (N=152)	Total-Adult (N=475)	Pediatric (N=29)	Total (N=504)
Total number of deaths	35 (31.0%)	36 (17.1%)	41 (27.0%)	112 (23.6%)	11 (37.9%)	123 (24.4%)
Death within 30 days of last dose of entrectinib						
Total number of deaths	14 (12.4%)	24 (11.4%)	17 (11.2%)	55 (11.6%)	4 (13.8%)	59 (11.7%)
Progressive Disease	8 (7.1%)	17 (8.1%)	10 (6.6%)	35 (7.4%)	4 (13.8%)	39 (7.7%)
Other	5 (4.4%)	4 (1.9%)	2 (1.3%)	11 (2.3%)	0	11 (2.2%)
Unknown	1 (0.9%)	3 (1.4%)	5 (3.3%)	9 (1.9%)	0	9 (1.8%)
Death more than 30 days after last dose of entrectinib						
Total number of deaths	21 (18.6%)	12 (5.7%)	24 (15.8%)	57 (12.0%)	7 (24.1%)	64 (12.7%)
Progressive Disease	19 (16.8%)	11 (5.2%)	14 (9.2%)	44 (9.3%)	7 (24.1%)	51 (10.1%)
Unknown	1 (0.9%)	1 (0.5%)	10 (6.6%)	12 (2.5%)	0	12 (2.4%)
Other	1 (0.9%)	0	0	1 (0.2%)	0	1 (0.2%)

Adult patients are defined as subject>=18 years of age; Pediatric patients are defined as subjects <18 year of age
Cause of death is defined differently for each study:
ALKA - 'Progressive Disease' if selected by investigator, 'Unknown' if selected by investigator or no cause given, 'Other' for any other reason.
STARTRK-1 - Cause of death was not collected (all 'Unknown').
STARTRK-2 and STARTRK-NG - 'Progressive Disease' if death is related to cancer, 'Other if death is not related to cancer, 'Unknown' if death has unknown relation to cancer.

An aggregate review of all grade 5 AEs in both paediatric and adult patients reported in the Company Safety Database was performed with a data cut-off date of 1 March 2020. In total, there were 45 fatal events reported: 30 events from clinical studies, 14 events from non-interventional studies/programs,

and 1 event from a spontaneous report. 43 fatal AEs were reported in adult patients and 2 fatal AEs were reported in paediatric patients treated with entrectinib (both from non-interventional studies/programs).

Compared to the analysis in the safety update report dated November 2019 (Clinical cutoff date: 31 October 2018, N= 504), five additional Grade 5 AEs occurred in adult patients in clinical trials, which included fatal events of hypoxia, pulmonary embolism, atrioventricular block, cerebrovascular accident, and death (1 event each). There have been no Grade 5 AEs reported in paediatric clinical trials.

Consistently with the fatal events observed in the previous Safety Update Reports, there were no patterns with respect to the type of Grade 5 AEs reported seen, and the majority of Grade 5 AEs were reported in the context of worsening of underlying disease or complications of the underlying malignancy.

Laboratory findings

Hematology

The majority of patients who experienced post baseline shifts in hematology parameters had shifts to Grade 1 or 2. Few patients had clinically relevant shifts (defined as change from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline) with the most common (n=35 patients) being Grade 3 low lymphocytes levels, followed by Grade 3 low hemoglobin (n=30 patients) and Grade 3 low neutrophils (n=21 patients). The laboratory value changes were transient and returned to baseline.

Clinically relevant hematology laboratory abnormalities that were reported as AEs (i.e., Grade 3 or 4 hematology AEs) occurred in few patients in the overall safety population, with the most common (≥ 2.0% of patients in the overall safety population) being Grade 3 anemia (10.7%), neutropenia (2.5%), and neutrophil count decreased (2.3%).

Chemistry

In the updated safety population (CCOD: 31 October 2018), the majority of patients who experienced post-baseline shifts in chemistry parameters had shifts from baseline grade to Grade 1 or 2. Few patients had clinically relevant treatment-emergent worsening to Grade 3 or 4 laboratory parameters (defined as change from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline) with the most common (≥2% of patients) being low phosphorus (5.9%), followed by low albumin (3.8%; all Grade 3), high AST, high glucose and low sodium (3.3% each), high ALT and high creatinine (3.1% each) and low calcium and low potassium (2.1% each). The laboratory value changes were transient and returned to baseline. The proportion of patients with shifts (both all grade and Grade 3 or 4) in liver laboratory parameters (AST increased, ALT increased, and bilirubin increased), based on the expanded safety population in the current analyses, was consistent with the previous analyses. All grade shifts (worsening from baseline) in elevated uric acid (hyperuricemia) was reported in 194 (50.8%) patients and Grade 3 or 4 shifts in elevated uric acid was reported in 26 (6.8%) patients in the integrated safety population. Of the 26 patients who had Grade 3 or 4 hyperuricemia, 9 patients were treated with urate-lowering medication allopurinol. The median time to event onset of increased blood uric acid of all grade was 0.95 months (range: 0.23-13.77 months).

Liver Laboratory Evaluations

The majority of patients who experienced post baseline shifts in liver laboratory parameters (AST increased, ALT increased, and bilirubin increased) had shifts to Grade 1 or 2. Few patients had clinically relevant shifts in (defined as change from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline): Grade 3 ALT increased (9 patients) and Grade 3 AST increased (8 patients).

Overall, the incidence of liver laboratory abnormalities reported as AEs was higher in the paediatric analysis set compared to the overall adult population, primarily driven by higher rate of AST increased and ALT increased.

Five (1.4%) patients in the overall integrated safety population met the laboratory abnormalities of ALT or AST ($> 3 \times$ ULN) in combination with an elevated total bilirubin ($> 2 \times$ ULN). Upon medical review, baseline liver metastasis or other confounding factors (such as medical history of liver or disease progression with new liver lesions) have been reported in all 5 patients; as such none of the liver enzyme abnormalities observed was indicative of drug induced liver injury.

Weight and Body Mass Index

A trend of body weight increase has been observed in patients treated with entrectinib. This observation is likely an on-target effect of entrectinib, as TRKB appears to be associated with appetite control. Based on available data on body weight, 65.6% (233/355) of patients experienced weight increase of ≥5% in the overall integrated safety population. A total of 99 (27.9%) patients experienced Grade 2 (10% to <20% increase) post-baseline weight increase and 63 (17.7%) patients experienced Grade 3 (≥20%) post-baseline weight increase. Few patients experienced weight decrease to Grade 1 post baseline (7.3%) and Grade 2 post baseline (1.7%).

Based on available data on BMI, in the overall integrated safety population, a total of 54 patients with normal BMI at baseline had their BMI shifted to overweight or obese category post baseline (n=51 and n=3, respectively). One patient with baseline BMI <18 kg/m2 (underweight) experienced a BMI shift to overweight category post baseline.

Electrocardiography

In Study STARTRK-2, ECGs were performed in triplicate and assessed by a central reader for all US and Japan sites. For all other sites, ECGs were performed locally and in single observation.

Triplicate Observations

Approximately half of the patients with triplicate ECG readings had a reading of QTcF interval at baseline. Of these patients, the majority (n=99) had normal QTcF interval at baseline ≤ 450 msec. No patient had a baseline QTcF interval ≥500 msec. After receiving treatment with entrectinib, the majority of patients (n=98) continued to have normal post-baseline QTcF interval ≤ 450 msec. One patient had QTcF interval >500 msec post-baseline and 4 patients had maximum QTcF increase from baseline > 60 msec.

Singular Observations

Approximately half of the patients with singular ECG reading had a reading of QTcF interval at baseline. Of these patients, the majority (n=89) had normal QTcF interval at baseline ≤ 450 msec. No patient had a baseline QTcF interval ≥500 msec. After receiving treatment with entrectinib, the majority of patients (n=81) continued to have normal QTcF interval post-baseline ≤450 msec. One patient had QTcF interval >480 $\leq$ 500 msec and 3 patients had maximum QTcF increase from baseline >60 msec.

In Study STARTRK-2, 3 (1.5%) patients had AE of electrocardiogram QT prolonged. Two events were Grade 1 and 1 event was Grade 3 in severity. One event of electrocardiogram QT prolonged led to entrectinib dose reduction. The other 2 events did not lead to entrectinib dose interruption or reduction. All 3 events were considered related to entrectinib by the investigator.

The relationship between entrectinib plasma concentrations and ECG data was further assessed in a PK-QT sub-study on a subset of patients from Study STARTRK-2. The results showed no evidence that

entrectinib causes any clinically relevant QTcF prolongation, but indicated a shortening of the QT-interval with increasing concentration of entrectinib.

In Study STARTRK-1, 5 patients had QTcF interval >450 msec post-baseline and 1 patient each had QTcF interval >480 msec and >500 msec post-baseline, respectively. Four patients had QTcF increase from baseline >60 msec. In Study STARTRK-1, 2 (2.6%) patients had AE of electrocardiogram QT prolonged. These events resolved without entrectinib dose interruption or reduction. Both events were considered related to entrectinib by the investigator.

In Study STARTRK-NG, the majority of patients (12 patients) had normal QTc values (≤450 msec) at baseline and throughout the study. Among the other 4 patients who had a baseline QTc values within the category of >450 to ≤480 msec, one patient had normal post-baseline QTc values; the remaining 3 patients each had maximum post-baseline QTc values reported in the category of >450 to ≤480 msec, >480 to ≤500, and >500 msec, respectively. Overall, the maximum QTc change from baseline reported in the majority of patients (13 patients) was ≤30 msec; 3 patients had a maximum QTc increase of >30 and ≤60 msec from baseline. All these events had no clinical impact and resolved without treatment and no action was taken with entrectinib. Two (12.5%) patients had AE of QT prolonged and 1 (6.3%) patient had AE of electrocardiogram QT shortened. All of these events were Grade 1 or Grade 2 in severity. These ECG abnormalities reported in the study all occurred in patients with pre-existing abnormalities. All these events resolved without treatment and no action was taken with entrectinib.

In Study ALKA, ECG data were performed locally and only collected limited information on the CRFs. QTc evaluation was performed at baseline and during treatment in 46 patients. There was no evidence of QC/QTc interval prolongation. No patient had a QTc value greater than 480 msec. Two patients had a QTc value ≥450 msec. In both cases, no AE of prolonged QTc interval was reported and treatment continued without intervention. One patient had QTc increase from baseline >60 msec. No AE of prolonged QTc interval was reported for this patient.

For the integrated analysis, the majority (58.6%) patients had normal QTc values (≤ 450 msec) at baseline and throughout the study. Six patients (1.7%) had QTc interval >500 msec post-baseline, and 10 patients had maximum QTc increase from baseline > 60 msec.

Safety in special populations

Age

The overall safety profile of entrectinib across all age groups is summarized in the table below.

Table 88: Overview of Safety by Age (CCOD: 31 October 2018, safety evaluable patients)

Safety Summary by Age (<18 years, 18 to 64 years, >= 65 years), Safety-Evaluable Patients
Protocols: GO40782, GO40783, GO40784, CO40778
CCOD: Oct 31 2018, DBL: Dec 21 2018

	Total (N=504)		
	Age Category		
	<18 years (N=29)	18 to 64 years (N=345)	>= 65 years (N=130)
Patients with AE	29 (100.0%)	344 (99.7%)	126 (96.9%)
Patients with Related AE	26 (89.7%)	320 (92.8%)	112 (86.2%)
Patients with Serious AE	10 (34.5%)	140 (40.6%)	51 (39.2%)
Patients with Related Serious AE	2 (6.9%)	32 (9.3%)	15 (11.5%)
Patients with NCI-CTCAE >= Grade 3 AE	16 (55.2%)	218 (63.2%)	74 (56.9%)
Patients with Related NCI-CTCAE >= Grade 3 AE	7 (24.1%)	114 (33.0%)	41 (31.5%)
Patients with AE Leading to Discontinuation	2 (6.9%)	28 (8.1%)	16 (12.3%)
Patients with Related AE Leading to Discontinuation	1 (3.4%)	13 (3.8%)	9 (6.9%)
Patients with AE Leading to Dose Reduction	10 (34.5%)	81 (23.5%)	40 (30.8%)
Patients with Related AE Leading to Dose Reduction	8 (27.6%)	80 (23.2%)	36 (27.7%)
Patients with AE Leading to Death	0	21 (6.1%)	3 (2.3%)

Investigator text for AEs encoded using MedDRA version 21.1.
Includes AEs with start date on or after the date of first dose of study treatment and up to and including 30 days after the last dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.

Thirty four (34) patients (6.7%) were 75 years or older. In patients <18 years of age, a lower frequency (11.8%) of SAEs was observed compared to those 18–64 years and ≥ 65 years (42.3% and 33.3%, respectively). Additionally, there were no deaths or AEs leading to study drug withdrawal reported for patients <18 years of age.

ECOG

Overall, the safety profile of entrectinib in adults across all baseline ECOG status is summarized in the table below.

Table 89: Overview of Safety by ECOG Performance at Baseline (CCOD: 31 October 2018, safety evaluable patients)

Safety Summary by ECOG Performance at Baseline (0, 1, and 2 or higher), Safety-Evaluable Patients
Protocols: GO40782, GO40783, GO40784, CO40778
CCOD: Oct 31 2018, DBL: Dec 21 2018

	Total (N=504)			
	Baseline ECOG Status			
	Missing (N=30)	0 (N=199)	1 (N=233)	2 or higher (N=42)
Patients with AE	30 (100.0%)	198 (99.5%)	230 (98.7%)	41 (97.6%)
Patients with Related AE	27 (90.0%)	191 (96.0%)	210 (90.1%)	30 (71.4%)
Patients with Serious AE	9 (30.0%)	59 (29.6%)	108 (46.4%)	25 (59.5%)
Patients with Related Serious AE	2 (6.7%)	15 (7.5%)	26 (11.2%)	6 (14.3%)
Patients with NCI-CTCAE >= Grade 3 AE	17 (56.7%)	103 (51.8%)	156 (67.0%)	32 (76.2%)
Patients with Related NCI-CTCAE >= Grade 3 AE	7 (23.3%)	62 (31.2%)	79 (33.9%)	14 (33.3%)
Patients with AE Leading to Discontinuation	2 (6.7%)	12 (6.0%)	21 (9.0%)	11 (26.2%)
Patients with Related AE Leading to Discontinuation	1 (3.3%)	9 (4.5%)	10 (4.3%)	3 (7.1%)
Patients with AE Leading to Dose Reduction	11 (36.7%)	53 (26.6%)	62 (26.6%)	5 (11.9%)
Patients with Related AE Leading to Dose Reduction	9 (30.0%)	51 (25.6%)	59 (25.3%)	5 (11.9%)
Patients with AE Leading to Death	0	2 (1.0%)	15 (6.4%)	7 (16.7%)

Investigator text for AEs encoded using MedDRA version 21.1.
Includes AEs with start date on or after the date of first dose of study treatment and up to and including 30 days after the last dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.

Program: root/clinical_studies/RO7102122/share/pool_D120/prod/program/t_saf_sum_by.sas
Output: root/clinical_studies/RO7102122/share/pool_D120/prod/output/t_saf_sum_bY_BYECOG_SE.out
04SEP2019 10:05
Of 30 missing ECOG PS at baseline, 29 patients were enrolled in STARTRK-NG and had their performance status measured by Karnofsky or Lansky scales.

Consistent with the impact of the overall underlying disease burden on a patient's general performance, a higher proportion of patients experienced SAEs, Grade ≥3 AEs, AEs leading to discontinuation, and deaths with higher ECOG performance status at baseline.

Central Nervous System Metastases

The safety profile of entrectinib in patients with CNS metastases is summarized in Table below.

Table 90: Overview of Neurological Toxicity AEs by CNS Metastases at Baseline (CCOD: 31 October 2018, safety evaluable patients)

Neurological Toxicity Safety Summary by CNS Disease at Baseline, Safety-Evaluable Patients
Protocols: GO40782, GO40783, GO40784, CO40778
CCOD: Oct 31 2018, DBL: Dec 21 2018

	Patients without CNS Disease at Baseline (N=328)	Patients with CNS Disease at Baseline (N=176)
Patients with AE	295 (89.9%)	149 (84.7%)
Patients with Related AE	256 (78.0%)	116 (65.9%)
Patients with Serious AE	27 (8.2%)	34 (19.3%)
Patients with Related Serious AE	11 (3.4%)	8 (4.5%)
Patients with NCI-CTCAE >= Grade 3 AE	42 (12.8%)	45 (25.6%)
Patients with Related NCI-CTCAE >= Grade 3 AE	18 (5.5%)	12 (6.8%)
Patients with AE Leading to Discontinuation	5 (1.5%)	2 (1.1%)
Patients with Related AE Leading to Discontinuation	4 (1.2%)	2 (1.1%)
Patients with AE Leading to Dose Reduction	36 (11.0%)	23 (13.1%)
Patients with Related AE Leading to Dose Reduction	32 (9.8%)	21 (11.9%)
Patients with AE Leading to Drug Interruption	52 (15.9%)	30 (17.0%)
Patients with Related AE Leading to Drug Interruption	41 (12.5%)	15 (8.5%)
Patients with AE Leading to Death	1 (0.3%)	3 (1.7%)

Investigator text for AEs encoded using MedDRA version 21.1.
CNS disease includes CNS metastases or primary brain tumors.

Neurological Toxicity Safety Summary by CNS Metastases at Baseline, Safety-Evaluable Patients
Protocols: GO40782, GO40783, GO40784, CO40778
Enrollment cutoff: Nov 30 2017, CCOD: May 31 2018, DBL: Jul 31 2018

Patients with CNS metastases at baseline did not have a higher rate of AEs than those without, however, a higher proportion of patients with CNS metastases experienced SAEs and Grade ≥3 AEs.

Geographical Region

Grade 3 above AE, AE leading to discontinuation, and AE leading to dose reduction were observed in lower frequencies in the Europe compared with Asia-Pacific and North America. The frequencies of all AE, SAE, and AE leading to death were observed similarly across all regions.

Safety related to drug-drug interactions and other interactions

(see section on clinical pharmacology)

Discontinuation due to adverse events

AEs that led to withdrawal, dose interruption and/or dose reduction

In the updated safety population (CCOD: 31 October 2018), a small proportion of patients (46/504 [9.1%]) had AEs that led to study drug discontinuation in the overall integrated safety population. AEs leading to withdrawal were most frequently reported (≥ 1% of patients) in SOCs of respiratory thoracic and mediastinal disorders (2.2%), cardiac disorders (1.8%), general disorders and administration site conditions (1.6%), and nervous system disorders (1.2%). There was no predominant AE PT that led to withdrawal of entrectinib.

A total of 231 (45.8%) patients experienced at least one AE that led to a dose interruption of entrectinib. By PT, the most frequently reported AEs leading to entrectinib dose interruption (≥ 1% of patients) were blood creatinine increased (4.4%), fatigue (4.2%) dizziness (4.0%), anemia (3.4%), pneumonia (3.1%), diarrhea and anemia (2.8% each), pyrexia, and dyspnea (2.5% each), nausea (2.3% each), AST increased and ALT increased, diarrhea and pneumonia (2.4% each), cognitive

disorder and nausea (2.2% each), pyrexia and dyspnea (2.0% each), neutrophil count decreased and edema peripheral (1.8% each), urinary tract infection (1.6%), vomiting, pleural effusion and hypotension (1.4% each) ataxia and lipase increased (1.2% each).

A total of 131 (26.0%) patients experienced at least one AE that led to a dose reduction. By PT, the most frequently reported AEs leading to entrectinib dose reduction (≥ 1% of patients) were dizziness (4.4%), fatigue (2.8%), blood creatinine increased (2.4%), gait disturbance (1.8%), weight increased (1.4%) and anemia (1.2%).

Paediatric safety data (CCOD: 1 November 2019)

The safety results provided herein are presented for an integrated paediatric safety population of 32 patients aged <18 years enrolled up to 1 May 2019 in STARTRK-NG (30 patients) and STARTRK-2 (2 patients), studies. The analyses were based on safety data collected up to a clinical cut-off date (CCOD) of 1 November 2019 (see Table below).

Table 91: Paediatric analysis sets in reported analyses of the safety of entrectinib in paediatric patients

	Primary STARTRK-NG CSR	Safety Update Report (November 2019)	Current Safety Update Report (April 2020)
Study ECOD for patients included	30 November 2017	31 October 2018	1 May 2019
CCOD for analysis	31 May 2018[c]	31 October 2018	1 November 2019
Total Safety Population	**16[a]**	**29[b]**	**32[b]**
Patients <18 years of age	15	29	32
Patients with tumors harboring relevant gene fusions	3	14	17
NTRK1/2/3	1	7	9
ROS1	1	5	5
ALK[c]	1	2	3
Patients with tumors with no detectable relevant gene fusion[d]	13	15	15

ALK, anaplastic lymphoma kinase; CCOD, clinical cutoff date; CSR, clinical study report; ECOD, enrolment cutoff date; NTRK, neurotrophic tyrosine receptor kinase.

[a] One young adult patient >18 years enrolled in the Phase I dose escalation of STARTRK-NG was included in this analysis.

[b] Includes only patients aged <18 years from STARTRK-NG and STARTRK-2. Two young adult patients >18 years enrolled in STARTRK-NG were excluded, and two pediatric patients <18 years enrolled in STARTRK-2 were included in analysis.

[c] Enrolment of ALK patients has been discontinued since protocol amendment (Version 6)

[d] Includes patients with either point mutations, or no detected genetic alteration, in *NTRK1/2/3*, *ROS1* or *ALK* genes or no available molecular test result.

Patient status on study

As of the CCOD of 1 November 2019, 18 out of the 32 patients in the integrated paediatric safety population (56.3%) had discontinued from the study and 14 patients (43.8%) were still on study. The most common reason for study discontinuation was the death of the patient (66.7% [12/18]). Most of the patients who died had neuroblastomas for which the NTRK1/2/3, ROS1, or ALK gene alteration status was unknown.

Patient status on treatment

As of the CCOD, 26 patients (81.3%) had discontinued entrectinib treatment. The primary reason for discontinuation of entrectinib was disease progression (20 patients [76.9% of those who discontinued]). The patients continuing to receive entrectinib treatment were patients with identified relevant gene fusions who continue to derive benefit.

Demographics

The median age of patients enrolled in the integrated paediatric safety population was 7.0 years (range: 4 months-17 years). The majority of patients were in the age group of ≥2 to <12 years (23 patients [71.9%]). Males and females were equally represented (16 patients each [50.0%]). Most patients were white (28 patients [87.5%]) and not Hispanic or Latino ethnicity (25 patients [78.1%]). The majority (22 patients [68.8%]) had a Karnofsky/Lansky performance score of at least 90 at screening.

Baseline Disease Characteristics

The most common tumour types diagnosed at study entry in the 32 patients in the integrated paediatric safety population were neuroblastomas (13 patients, with an additional 2 patients with ganglioneuroblastomas), followed by primary CNS tumours (glioblastomas [3], gliomas [2], anaplastic ganglioglioma [1], anaplastic astrocytoma [1], desmoplastic infantile astrocytoma [1], and glioneuronal tumour [1]), sarcomas (all inflammatory myofibroblastic tumours [3]), infantile fibrosarcoma (2). The other tumour types were NSCLC (not otherwise specified), salivary carcinoma (MASC), and melanoma (metastatic to lung), represented in single patients. Fifteen patients (48.4%) had Stage IV tumours at initial diagnosis, and 18 patients (56.3%) presented with metastatic disease at baseline, most commonly affecting bone and lung. Three patients, all with neuroblastomas, had brain metastases at baseline. Molecular testing identified 17 patients with tumours harbouring positive gene fusions (9 NTRK1/2/3, 5 ROS1 and 3 ALK genes) and 2 patients with point mutations. The remaining 15 patients had either no detected genetic alteration in NTRK1/2/3, ROS1 or ALK genes or no available molecular test result.

Safety data

An overall summary of treatment-emergent AEs reported by category for all patients treated with entrectinib in the integrated paediatric safety evaluable population (n=32) is shown in Table below.

Table 92: Overview of adverse events in paediatric safety population

	Primary STARTRK-NG CSR	Safety Update Report (November 2019)	Current Safety Update Report (April 2020)
Study ECOD for patients included	30 November 2017	31 October 2018	1 May 2019
CCOD for analysis	31 May 2018	31 October 2018	1 November 2019
Patients with at least one:	**Total N=16[a]**	**Total N=29[b]**	**Total N=32[b]**
Any AEs	16 (100%)	29 (100%)	32 (100%)
Serious AEs	2 (12.5%)	10 (34.5%)	14 (43.8%)
Grade ≥3 AE	8 (50%)	16 (55.2%)	21 (65.6%)
AE Leading to discontinuation	1 (6.3%)	2 (6.9%)	3 (9.4%)
AEs Leading to dose reduction	4 (25.0%)	10 (34.5%)	11 (34.4%)
AEs leading to dose interruption	4 (25.0%)	12 (41.4%)	15 (46.9%)
AEs leading to death	0	0	0

AE, adverse event; CCOD, clinical cutoff date; CSR, clinical study report; ECOD, enrolment cutoff date.

[a] One young adult patient aged >18 years enrolled in the Phase I dose escalation of STARTRK-NG was included in this analysis.

[b] Includes only patients aged <18 years from STARTRK-NG and STARTRK-2. Two young adult patients aged >18 years enrolled in STARTRK-NG were excluded, and two pediatric patients aged <18 years enrolled in STARTRK-2 were included in analysis.

Extent of exposure to study treatment

Table 93: Extent of exposure to entrectinib in paediatric safety population

	Primary STARTRK-NG CSR	Safety Update Report (November 2019)	Current Safety Update Report (April 2020)
Study ECOD for patients included	30 November 2017	31 October 2018	1 May 2019
CCOD for analysis	31 May 2018	31 October 2018	1 November 2019
Patients with at least one:	**Total N=16[a]**	**Total N=29[b]**	**Total N=32[b]**
Treatment duration (months)			
median (range)	1.9 (0.2, 12.9)	3.0 (0.2, 17.7)	5.6 (0.2, 29.8)
Total cumulative dose, mg			
mean (SD)	68,800 (108465)	75,293 (107,515)	116,053 (156,584)
Dose intensity (%)[c],			
median (range)	96.3 (32.6, 115.1)	94.9 (28.8, 115.1)	96.3 (28.8, 120.5)

CCOD, clinical cutoff date; CSR, clinical study report; ECOD, enrolment cutoff date.

[a] One young adult patient aged >18 years enrolled in the Phase I dose escalation of STARTRK-NG was included in this analysis.

[b] Includes only patients aged <18 years from STARTRK-NG and STARTRK-2. Two young adult patients aged >18 years enrolled in STARTRK-NG were excluded, and two pediatric patients aged <18 years enrolled in STARTRK-2 were included in analysis.

[c] Defined as dose intensity [cumulative dose/number of planned doses] ÷ planned daily dose at the beginning of treatment × 100%.

The median treatment duration was longer in patients with tumours harbouring NTRK1/2/3, ROS1 or ALK gene fusions (11.7 months) compared to patients with no detectable relevant gene fusion (1.8 months), almost all being neuroblastoma patients who discontinued early from study treatment. This greater extent of exposure to entrectinib was reflective of a higher proportion of patients with gene fusions achieving durable objective responses and continuing to receive daily entrectinib treatment, as compared to patients with no detectable relevant gene fusion, (predominantly neuroblastoma patients) who discontinued treatment due to progressive disease.

Adverse drug reactions

Table 94: Adverse drug reactions occurring in paediatric patients treated with entrectinib in clinical trials

System organ class	Frequency	Adolescents[1] (N=7)	All paediatric patients (N=32)
Infections and infestations	Very common		Urinary tract infection (18.8), Lung infection (12.5%),
Blood and lymphatic system disorders	Very common	Anaemia (57.1%), Neutropenia (42.9%)	Anaemia (59.4%), Neutropenia (43.8%)
Metabolism and nutritional disorders	Very common	Weight increased (57.1%), Decreased appetite (14.3%)	Weight increased (50%), Decreased appetite (31.3%), Dehydration (25%)
Nervous system disorders	Very common	Dysgeusia (42.9%), Dysaesthesia (28.6%), Mood disorders (28.6%), Cognitive disorders (14.3%), Headache (14.3%), Syncope (14.3%), Peripheral sensory neuropathy (14.3%), Sleep disturbances (14.3%)	Headache (31.3%), Dysgeusia (21.9%), Mood disorders (28.1%), Ataxia (15.6%), Sleep disturbances (13.3%), Dizziness (12.5%), Peripheral sensory neuropathy (12.5%),
Eye disorders	Very common	Vision blurred (14.3%)	
Vascular disorders	Very common	Hypotension (14.3%)	Hypotension (18.8%)
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea (28.6%), Cough (28.6%)	Dyspnoea (18.8%), Cough (50%), Pleural effusion (12.5%)
Gastrointestinal disorders	Very common	Nausea (71.4%), Abdominal pain (28.6%), Constipation (28.6%)	Nausea (46.9%), Abdominal pain (28.1%), Constipation (43.8%), Vomiting (34.4%), Diarrhoea (37.5%)
Hepatobiliary disorders	Very common	AST increased (57.1%), ALT increased (42.9%)	AST increased (50%), ALT increased (50%)
Skin and subcutaneous tissue disorders	Very common		Rash (25%)
Musculoskeletal and connective tissue disorders	Very common	Arthralgia (14.3%), Myalgia (14.3%)	Fractures (21.9%)
	Very common	Muscular weakness (28.6%)	Muscular weakness (18.8%)
Renal and urinary disorders	Very common	Blood creatinine increased (57.1%)	Blood creatinine increased (43.8%), Urinary retention (21.9%)
General disorders and administration site conditions	Very common	Fatigue (42.9%), Pain (57.1%), Pyrexia (57.1%)	Fatigue (43.8%), Pain (46.9%), Pyrexia (56.3%), Oedema (18.8%)

% refers to all grades
[1]Adolescents (12 to <18 years of age): Grade ≥3 reactions reported were neutropenia and headache

Deaths

A total of 13 patients (40.6%) have died; the primary cause of death in every case was reported as progressive disease. There were no fatal AEs reported. Four of 13 patients died within 30 days of the last dose of entrectinib treatment. By tumour type, 9 of the 13 patients who died were neuroblastoma patients. The other four patients had salivary adenocarcinoma, anaplastic ganglioglioma, desmoplastic infantile astrocytoma and NSCLC-NOS . For the majority of patients who died, their NTRK1/2/3, ROS1, or ALK gene alteration status was unknown.

Serious adverse events (SAEs)

A total of 50 SAEs were reported in 14 of the 32 treated patients (43.8%) (see Table below).

Table 95: Serious adverse events in integrated paediatric safety population (CCOD: 1 November 2019; safety evaluable patients)

Protocols: GO40782, CO40778
CCOD: Nov 01 2019, DBL: Feb 10 2020

MedDRA System Organ Class MedDRA Preferred Term	Pediatric (N=32)
Total number of patients with at least one adverse event	14 (43.8%)
Overall total number of events	50
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one adverse event	6 (18.8%)
Total number of events	13
DEVICE RELATED INFECTION	2 (6.3%)
PNEUMONIA	2 (6.3%)
CATHETER SITE INFECTION	1 (3.1%)
ENCEPHALITIS	1 (3.1%)
LOWER RESPIRATORY TRACT INFECTION	1 (3.1%)
RESPIRATORY SYNCYTIAL VIRUS INFECTION	1 (3.1%)
RESPIRATORY TRACT INFECTION	1 (3.1%)
SEPSIS	1 (3.1%)
UPPER RESPIRATORY TRACT INFECTION	1 (3.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total number of patients with at least one adverse event	5 (15.6%)
Total number of events	16
DYSPNOEA	2 (6.3%)
HYPOXIA	2 (6.3%)
ALVEOLITIS	1 (3.1%)
ATELECTASIS	1 (3.1%)
BRONCHOSPASM	1 (3.1%)
PLEURAL EFFUSION	1 (3.1%)
PULMONARY OEDEMA	1 (3.1%)
RESPIRATORY ACIDOSIS	1 (3.1%)
RESPIRATORY FAILURE	1 (3.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one adverse event	4 (12.5%)
Total number of events	4
FEMUR FRACTURE	2 (6.3%)
RADIATION VASCULITIS	1 (3.1%)
THERMAL BURN	1 (3.1%)
GASTROINTESTINAL DISORDERS	
Total number of patients with at least one adverse event	3 (9.4%)
Total number of events	3
VOMITING	2 (6.3%)
PANCREATITIS	1 (3.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Total number of patients with at least one adverse event	3 (9.4%)
Total number of events	5
PYREXIA	2 (6.3%)
FACE OEDEMA	1 (3.1%)
GAIT DISTURBANCE	1 (3.1%)
PAIN	1 (3.1%)
NERVOUS SYSTEM DISORDERS	
Total number of patients with at least one adverse event	3 (9.4%)
Total number of events	3
HEADACHE	2 (6.3%)
DEPRESSED LEVEL OF CONSCIOUSNESS	1 (3.1%)
METABOLISM AND NUTRITION DISORDERS	
Total number of patients with at least one adverse event	1 (3.1%)
Total number of events	1
HYPONATRAEMIA	1 (3.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Total number of patients with at least one adverse event	1 (3.1%)
Total number of events	1

PATHOLOGICAL FRACTURE	1 (3.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	
Total number of patients with at least one adverse event	1 (3.1%)
Total number of events	1
GLIOMA	1 (3.1%)
PRODUCT ISSUES	
Total number of patients with at least one adverse event	1 (3.1%)
Total number of events	1
DEVICE FAILURE	1 (3.1%)
PSYCHIATRIC DISORDERS	
Total number of patients with at least one adverse event	1 (3.1%)
Total number of events	1
MANIA	1 (3.1%)
RENAL AND URINARY DISORDERS	
Total number of patients with at least one adverse event	1 (3.1%)
Total number of events	1
URINARY RETENTION	1 (3.1%)

Investigator text for AEs encoded using MedDRA version 22.1.
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.
Includes AEs with start date on or after the date of first dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.

Adverse events that led to withdrawal of entrectinib treatment

Three patients (3/32 [9.4%]) experienced AEs leading to discontinuation of entrectinib. Two events were previously reported in the previous Safety Update Report, dated November 2019: one non-serious Grade 3 dyspnoea and one serious Grade 4 pulmonary oedema. At the time of the current report, one additional patient withdrew from entrectinib due to serious Grade 4 pancreatitis. This pancreatitis event was considered related to entrectinib by the investigator and had not resolved. There was no general trend in the reporting of specific AEs leading to withdrawal.

Adverse events that led to entrectinib dose modification

A total of 16 AEs led to dose reduction of entrectinib in 11 patients (34.4%). By preferred term, weight increased (4 patients) and blood creatinine increased (2 patients) were the only AEs which led to dose reduction in more than one patient. In 13 of the 16 cases where entrectinib dose was reduced for an AE the event resolved.

A total of 133 AEs leading to dose interruption of entrectinib in 15 patients (46.9%). By preferred term neutrophil count decreased, diarrhoea and pyrexia were the only AEs which led to dose interruption is more than two patients (and three patients only).

Adverse events of special interest

Selected AEs defined by the Sponsor were defined on the basis of previous clinical experience, mechanism of action and safety profile from drugs with similar targets to provide a more comprehensive understanding of the paediatric safety profile of entrectinib. The same grouped terms that have been used for previous analyses were used in the current analysis of selected AEs.

Neurologic toxicity was observed in 87.5% (28/32, Grade ≥3 15.7%) of patients: the most common (i.e. ≥10%) AEs by preferred term (PT) were headache (31.3%, Grade ≥3 6.3%), dysgeusia (21.9%, none Grade ≥3), muscular weakness (18.8%, Grade ≥3 3.1%), photophobia (18.8%, none Grade ≥3), anxiety, insomnia, somnolence and urinary incontinence (15.6% each, none Grade ≥3), agitation, dizziness, enuresis, gait disturbance and irritability (12.5% each, Grade ≥3 gait disturbance AEs 6.3%).

Ataxia AEs were observed in 5/32 patients (15.6%, Grade ≥3 6.3%), peripheral sensory neuropathy AEs in 4/32 (12.5%, none Grade ≥3), cognitive disorders AEs in 3/32 (9.4%, Grade ≥3 3.1%),

dysesthesia AEs in 3/32 (9.4%, none Grade ≥3), syncope AEs in 3/32 (9.4%, Grade ≥3 6.3%), seizure AEs in 2/32 (6.3%, none Grade ≥3),

Elevated liver laboratory tests and other liver abnormalities were reported in 23 out of 32 patients (71.9%, Grade ≥3 9.4%), the most common (i.e. ≥10%) AEs by PT being ALT increased (50%, Grade ≥3 6.2%), AST increased (50%, Grade ≥3 6.2%) and hypoalbuminaemia (18.8%, Grade ≥3 3.1%). The majority of patients for whom elevated liver laboratory tests and other liver abnormalities AEs were reported, had Grade 1 events (46.9%) which resolved.

Haematologic AEs were observe in 68.8% (22/32, Grade ≥3 43.8%) of patients: the most common (i.e. ≥10%) AEs by PT were anaemia (59.4%, Grade ≥3 12.5%), neutrophil count decreased (40.6%, Grade ≥3 25%), white blood cell count decreased (34.4%, Grade ≥3 9.4%), platelet count decreased (21.9%, Grade ≥3 9.4%) and lymphocyte count decreased (18.8%, Grade ≥3 12.5%).

Increased creatinine and other renal AEs were reported in 22/32 patients (68.8%, Grade ≥3 3.1%) the most common (i.e. ≥10%) by PT being blood creatinine increased (43.8%, none Grade ≥3), haematuria (18.8%, none Grade ≥3), urinary tract infection (18.8%, Grade ≥3 3.1%), pollakiuria (15.6%, none Grade ≥3), proteinuria (15.6%, none Grade ≥3), urinary incontinence (15.6%, none Grade ≥3) and enuresis (12.5%, Grade ≥3 12.5%).

Changes in weight AEs were observed in 17/32 patients (53.1%, Grade ≥3 25%), and the most common (i.e. ≥10%) AE by PT was weight increased (50.0%). The majority (13/32 patients [40.6%]) of weight increased events were assessed as related to entrectinib. Grade 1 or Grade 2 weight increased were reported in 9/32 patients (28.2%). Grade 3 weight increased was reported in 7/32 patients (21.9%). Four of 7 patients with Grade 3 weight increased were able to continue entrectinib without dose modifications. One Grade 3 AE of weight decreased (by PT) was reported.

A change from baseline in BMI category was measured in 50.0% (16/32) of patients while receiving entrectinib treatment. Treatment-emergent shifts (increases) in body-mass index (BMI) category were observed for 13 patients who were underweight at baseline (to normal, overweight and obese categories), 2 patients who were of normal weight at baseline (to overweight or obese categories) and 1 patient who was overweight at baseline (to obese category).

Eye disorders AEs were reported in 15/32 patients (46.9%, Grade ≥3 3.1%), the most common (i.e. ≥10%) by PT being photophobia(18.8%, none Grade ≥3) and eye pain (12.5%, none Grade ≥3).

Qt interval prolongation AEs in 2/32 (6.3%, none Grade ≥3). All patients met the eligibility criteria of having electrocardiogram corrected QT intervals (QTc; determined using Fridericia's or Bazett's formula) of ≤480 msec. The majority (24/32 [92.3%]) of patients had normal QTc values (≤450 msec) at baseline and of these, all except two patients (with maximum post-baseline QTc intervals of >450 and ≤480 msec and >480 and ≤500 msec, respectively), maintained normal QTc intervals throughout the study. For the majority (23/32 [74.2%]) of patients, the maximum QTc interval increase from baseline was ≤30 msec; six patients had a maximum QTc increase of between 30 and 60 msec and two patients had an increase exceeding 60 msec.

Congestive heart failure AEs in 1/32 (3.1%, Grade ≥3 3.1%) and pneumonitis AEs 1/32 (3.1%, Grade ≥3 3.1%).

Fractures: In paediatric patients all fractures occurred in patients with minimal or no trauma. A total of 11 adverse reactions of fractures were reported in the 7 paediatric patients. The median time to fracture was 4.3 months (range: 2.46 months to 7.39 months) in paediatric patients. Rozlytrek was interrupted in 42.9% (3/7) of paediatric patients that experienced fractures. Three of the fractures were Grade 2 and 4 fractures were Grade 3. Three of the Grade 3 fractures were serious. There were no reports of tumour involvement at the site of the fracture. All but one event of fracture recovered. At

the time of the CCOD, the outcome of the majority of the fractures (in 6/7 patients [85.7%]) had resolved (see Table below).

Table 96: Listing of fractures in integrated paediatric safety population (CCOD; 1 November 2019)

Patient ID	Age/Sex	Gene alteration	Preferred term	NCI CTC AE Grade	Onset time (Study Day)	Action taken	Outcome
		unknown	Femur fracture	2	75	Dose not changed	Recovered
			Femur fracture*	3	84	Drug interrupted	Recovered
			Fibula fracture	2	177	NA	Not recovered
		unknown	Tibia fracture	2	225	Dose not changed	Recovered
			Tibia fracture	3	297	Dose not changed	Recovered
		TFG-ROS1	Foot fracture	2	130	Dose not changed	Recovered
		ALK F1174L	Tibia fracture	2	121	Dose not changed	Recovering
		ARHGEF2-NTRK1	Fibula fracture	2	175[a]	Dose not changed	Recovered
		EML1-NTRK2	Femur fracture	1	221[a]	Dose not changed	Recovered
			Femur fracture*	3	221[a]	Drug interrupted	Recovered with sequelae
		GOPC-ROS1	Pathological fracture	1	85	Dose not changed	Recovered
			Pathological fracture*	3	86	Drug interrupted	Recovered with sequelae

* Serious events.

[a] new event occurring after 31 October 2018, the CCOD used for the previous Safety Update Report (dated November 2019).

Post marketing experience

Data were retrieved for all spontaneous cases reported between the date of the first marketing authorization (Japan, 18 June 2019) and 7 October 2019.

Data for 8 patients, reporting 34 events were retrieved. The review of the reported events identified that in 7/8 cases, the onset of the events was before the first marketing authorization of entrectinib, which indicates, that these events, while being reported via spontaneous sources, represent events occurring in the clinical trials or compassionate use programs with entrectinib. One case reported events of peripheral edema, with onset date in October 2019, which represents the only report from the post marketing settings. All events were reported once and 22/34 of the reported events were serious.

Table 97: Overview on Adverse Events on PT and SOC Level from Spontaneous Reporting (18 June 2019 to 7 October 2019 Inclusive)

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
System Organ Class	**Preferred Term**					
Infections and infestations	Abdominal abscess	1	1	4.5	1	2.9
	Infection	1	1	4.5	1	2.9
	Klebsiella infection	1	1	4.5	1	2.9
	Meningitis	1	1	4.5	1	2.9
	Respiratory syncytial virus infection	1	1	4.5	1	2.9
	Sepsis	1	1	4.5	1	2.9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Infected neoplasm	1	1	4.5	1	2.9
	Neoplasm recurrence	1	1	4.5	1	2.9
Blood and lymphatic system disorders	Blood disorder	1	1	4.5	1	2.9
Nervous system disorders	Cerebrovascular accident	1	1	4.5	1	2.9
	Dizziness	1	0	0.0	1	2.9
	Dysaesthesia	1	1	4.5	1	2.9
Eye disorders	Eye pain	1	0	0.0	1	2.9
Cardiac disorders	Cardiac disorder	1	0	0.0	1	2.9
	Cardiac failure congestive	1	1	4.5	1	2.9
Respiratory, thoracic and mediastinal disorders	Pneumonia aspiration	1	1	4.5	1	2.9
	Pulmonary congestion	1	1	4.5	1	2.9
Gastrointestinal disorders	Abdominal discomfort	1	0	0.0	1	2.9
	Abdominal pain upper	1	1	4.5	1	2.9
	Hypoaesthesia oral	1	0	0.0	1	2.9
Musculoskeletal and connective tissue disorders	Myalgia	1	0	0.0	1	2.9
	Rotator cuff syndrome	1	1	4.5	1	2.9
General disorders and administration site conditions	Feeling abnormal	1	1	4.5	1	2.9
	Inflammation	1	0	0.0	1	2.9
	No adverse event	1	0	0.0	1	2.9
	Oedema peripheral	1	0	0.0	1	2.9
	Pseudocyst	1	1	4.5	1	2.9
	Therapeutic product effect decreased	1	0	0.0	1	2.9
Investigations	Neutrophil count decreased	1	0	0.0	1	2.9
	Platelet count decreased	1	0	0.0	1	2.9
	Weight increased	1	1	4.5	1	2.9
Injury, poisoning and procedural complications	Muscle injury	1	1	4.5	1	2.9
	Muscle rupture	1	1	4.5	1	2.9
Surgical and medical procedures	Abscess drainage	1	1	4.5	1	2.9
Total		**N/A**	**22**	**100.0**	**34**	**100.0**

The outcome of the events was not reported or unknown for the majority of the reported events (25/34 events), was recovered / resolved for 4/34 events, not recovered/ not resolved for 2/34 events

and recovering / resolving for 1/34 events. Events, which were reported as not recovered / not resolved were Infection and Neoplasm recurrence. No events with fatal outcome were reported.

The reported events were in line with the known safety profile of entrectinib or could be expected in the patient population with advanced malignancies.

The Applicant additionally retrieved data reported to the safety database from non interventional program/studies (NIP/NIS), retrieved for all NIP/NIS cases as of 8 October 2019.

Data for 13 patients, reporting 72 events were retrieved. The majority of the events were reported once with exception of dizziness (reported in 4 patients), malaise (reported in 3 patients), constipation (3 patients) and anemia, dysphagia, nausea, fatigue, gait disturbance, pain, AST increased, blood creatinine increased and weight increased (each reported in 2 patients). Nineteen out of 72 of the reported events were serious. The summary of the reported events is presented in Table below.

Table 98: Overview on Adverse Events on PT and SOC level from Non Interventional Program / Studies

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
System Organ Class	**Preferred Term**					
	Pneumonia	1	1	5.3	1	1.4
Infections and infestations	Upper respiratory tract infection	1	0	0.0	1	1.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Glioma	1	1	5.3	1	1.4
Blood and lymphatic system disorders	Anaemia	2	0	0.0	2	2.8
Endocrine disorders	Adrenal insufficiency	1	1	5.3	1	1.4
	Precocious puberty	1	0	0.0	1	1.4
Metabolism and nutrition disorders	Decreased appetite	1	0	0.0	1	1.4
	Hypernatraemia	1	0	0.0	1	1.4
	Hypoalbuminaemia	1	0	0.0	1	1.4
	Hypoglycaemia	1	0	0.0	1	1.4
	Hypokalaemia	1	1	5.3	1	1.4
Psychiatric disorders	Mental status changes	1	1	5.3	1	1.4
Nervous system disorders	Cognitive disorder	1	0	0.0	1	1.4
	Dizziness	4	0	0.0	4	5.6
	Dysgeusia	1	0	0.0	1	1.4
	Headache	1	0	0.0	1	1.4
	Hypersomnia	1	0	0.0	1	1.4
	Paraesthesia	1	0	0.0	1	1.4
	Syncope	1	1	5.3	1	1.4
Eye disorders	Asthenopia	1	0	0.0	1	1.4
Ear and labyrinth disorders	Vertigo	1	0	0.0	1	1.4
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1	0	0.0	1	1.4
	Hypoxia	1	1	5.3	1	1.4
	Pulmonary amyloidosis	1	1	5.3	1	1.4
	Pulmonary embolism	1	1	5.3	1	1.4
	Respiratory failure	1	1	5.3	1	1.4
Gastrointestinal disorders	Abdominal pain	1	0	0.0	1	1.4
	Constipation	3	1	5.3	4	5.6
	Diarrhoea	1	0	0.0	1	1.4
	Dysphagia	2	1	5.3	2	2.8
	Flatulence	1	0	0.0	1	1.4
	Nausea	2	0	0.0	2	2.8
Skin and subcutaneous tissue disorders	Hypertrichosis	1	0	0.0	1	1.4
Musculoskeletal and connective tissue disorders	Muscular weakness	1	1	5.3	1	1.4
	Pain in extremity	1	0	0.0	1	1.4
	Pain in jaw	1	0	0.0	1	1.4
General disorders and administration site conditions	Asthenia	1	1	5.3	1	1.4
	Chest pain	1	1	5.3	1	1.4
	Death	1	1	5.3	1	1.4
	Fatigue	2	1	5.3	2	2.8

	Gait disturbance	2	0	0.0	2	2.8
	General physical health deterioration	1	1	5.3	1	1.4
	Malaise	3	0	0.0	3	4.2
	Oedema	1	0	0.0	1	1.4
	Oedema peripheral	1	0	0.0	1	1.4
	Pain	2	0	0.0	2	2.8
	Pyrexia	1	0	0.0	1	1.4
Investigations	Alanine aminotransferase increased	1	0	0.0	1	1.4
	Aspartate aminotransferase increased	2	0	0.0	2	2.8
	Blood alkaline phosphatase increased	1	0	0.0	1	1.4
	Blood creatinine increased	2	0	0.0	2	2.8
	Lymphocyte count decreased	1	0	0.0	1	1.4
	Weight increased	2	0	0.0	2	2.8
	White blood cell count decreased	1	0	0.0	1	1.4
Injury, poisoning and procedural complications	Fall	1	1	5.3	1	1.4
Total		**N/A**	**19**	**100.0**	**72**	**100.0**

The outcome of the events was reported as recovered / resolved for 21/72 events, not recovered/ not resolved for 20/72 events, was not reported for 26/72 events and was recovering / resolving for 1/72 events. Three events (in 2 patients) were reported with fatal outcome: death (in 1 patient) and glioma and respiratory failure (in 1 patient).

2.6.1. Discussion on clinical safety

The **integrated safety database** supporting the MAA of entrectinib in the broad claimed indication is comprised of 355 subjects who received at least one dose of entrectinib across 3 Phase I dose escalation/expansion studies (the ALKA and STARTRK-1 trials in adults and the STARTRK-NG study in children, adolescents and young adults) and one Phase II trial in adults (study STARTRK-2). All subjects in the integrated safety database were required to have at least 6 months of follow-up at the time of the data cut-off date (31 May 2018).

An updated safety report submitted during the procedure comprises cumulative data from 504 subjects, including 475 adult and 29 paediatric patients, irrespective of length of exposure and date of enrolment (data cut-off date October 31, 2018) provided only limited additional information to the already known safety profile of entrectinib.

Four distinct **safety analysis subsets** were identified by the Applicant based on type of genetic/molecular alteration (subjects with NTRK gene fusion positive malignancies [n=113], patients with ROS1 positive NSCLC [n=210], subjects outside the claimed indication i.e. with ROS1 positive non-NSCLC, ALK fusion positive solid tumours or with no gene fusion [n=152]) and age (paediatric subjects with or without TRK, ROS1, or ALK gene fusions/molecular alterations n=29).

Supportive safety data were also separately provided for 8 patients treated under a single-case compassionate use program and 14 adult patients from the PK Study RXDX-101-14. Data from all spontaneous cases (n=8) reported between the date of the first marketing authorization (Japan, 18 June 2019) and 7 October 2019, and from non interventional program/studies (NIP/NIS, n=13) as of 8 October 2019 were also submitted, together with safety data from healthy subjects exposed in clinical pharmacology studies.

Overall, the size of the entrectinib safety database in the claimed indication in adults (i.e. patients with NTRK gene fusion malignancies or ROS1 positive NSCLC) is considered of limited extent, yet in principle adequate due to the rarity of these genetic/molecular subtypes.

As a general concern, the uncontrolled design of all the studies included in the pooled analysis is not considered adequate to clearly disentangle signs/symptoms of the underlying malignancies and entrectinib-related adverse events (AEs), in this regard, limited help is provided by the short-term safety data available in healthy subjects who were exposed to a variety of entrectinib doses. The integrated safety population is also characterised by a significant heterogeneity in terms of age (min 4, max 86 years), type of underlying malignancy, dose administered (from 100 to 1600 mg/m^2/day, BSA-based vs. flat dose), drug regimen (4 days on/3 days off for 21 days in 28-day cycles vs. continuous daily dosing) and formulation that further complicates safety evaluations.

Median exposure to entrectinib was limited (5.5 months - 7 cycles), yet some patients were able to receive entrectinib up to 42 months. Treatment compliance is considered acceptable, with a median dose intensity as high as 96.5% and a low median number of missed doses (n=1). Median treatment duration was longer in subjects with NTRK gene fusions and ROS1 positive NSCLC (6.4 and 7.4 months, respectively).

Almost all subjects (99%) in the integrated safety population experienced at least 1 **treatment-emergent AE (TEAE)**, with the majority being considered as related (90.9%). **Grade ≥3 AEs** and **serious AEs (SAEs)** were experienced by 61.1% and 39.9% of patients, respectively, with only a minority of severe AEs/SAEs considered as treatment-related by the Investigator (32.1% and 9.7%, respectively). The incidence of AEs was generally consistent across all safety subsets, with the exception of a higher frequency of SAEs, Grade ≥3 AEs and AEs leading to death in the NTRK-adult subset. The clinical relevance of these findings has to be interpreted with caution, since differences across safety subsets in terms of exposure, dose, administration regimen, formulation, underlying malignancy, genetics and sample size might have impacted the data.

In the safety population, 9.1% (46/504) of patients experienced an AE that led to entrectinib discontinuation and cardiac and respiratory AEs represented the primary reason for discontinuation. Overall, the proportion of patients with AEs leading to treatment discontinuation is relatively low, and no pattern or cluster of AEs leading to discontinuation could be identified. Dose Interruptions and reduction were observed in 45.8% and 26% of patients, respectively, with no specific pattern of AEs identifiable.

The most common adverse reactions (≥ 20%) were fatigue, constipation, dysgeusia, oedema, dizziness, diarrhoea, nausea, dysaesthesia, dyspnoea, anaemia, increased weight, increased blood creatinine, pain, cognitive disorders, vomiting, cough, and pyrexia. The most frequent serious adverse reactions (≥ 2%) were lung infection (5.2%), dyspnoea (4.6%), cognitive impairment (3.8%), and pleural effusion (2.4%). Permanent discontinuation due to an adverse reaction occurred in 4.4% of patients.

Adverse reactions of Grade 3 or 4 severity occurring more frequently (at least a 5% increased incidence) in paediatric patients compared to adult patients were neutropenia (20.7% vs. 3.4%), weight increased (13.8% vs 6.9%), headache (6.9% vs 0.6%) and bone fractures (10.3% vs 1.9%) (see section 4.8 of the SmPC).

Overall, 123 subjects (24.4%) in the integrated safety population had died and in most cases (~70%) the reported reason for death was disease progression. Overall, at the time of the most updated analysis, 45 Grade 5 events reported: 30 fatal events from clinical studies, 14 from non-interventional studies/programs, and 1 from a spontaneous report. In particular, in the updated reports (last data cut-off date March 1, 2020), 8 additional grade 5 AEs were reported from clinical studies, which include

pulmonary embolism(2 events), and cardiac arrest, sudden death, hypoxia, pulmonary embolism, atrioventricular block, cerebrovascular accident, and death (1 event each). Among the 21 cases of fatal AEs initially reported, cardiac SOC AEs included 2 cases of cardio-respiratory arrest in patients with metastatic NSCLC and metastatic squamous cell carcinoma, respectively, and 1 case of cardiogenic shock due to pericardial effusion and pericardial tamponade in a patient with metastatic NSCLC. Overall, fatal AEs were reported in the context of advanced cancer or disease progression; no cluster or pattern with respect to the type of Grade 5 AEs is observed.

AEs of special interest

Neurologic AEs

In accordance with the entrectinib mechanism of action and widespread expression of TRK receptors in nervous tissues, **neurologic toxicity** was heterogeneous and involved both central and peripheral nervous systems. Except for seizures, all events were considered as related to entrectinib and are included in the SmPC. Reassuringly, most AEs were mild to moderate (Grade 1/2 70.8%) and did not result in high drug discontinuation rates. Impairment of neurodevelopment in paediatric patients is included in the RMP as an important potential risk.

Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials with Rozlytrek. Patients over the age of 65 years experienced a higher incidence of these events than younger patients. Patients should be monitored for signs of cognitive changes. Based on the severity of cognitive disorders, Rozlytrek treatment should be modified as described in section 4.2.of the SmPC. Patients should be counselled on the potential for cognitive changes with Rozlytrek treatment. Patients should be instructed not to drive or use machines until symptoms resolve if they experience cognitive disorders (see sections 4.2, 4.4, 4.7 and 4.8 of the SmPC).

Overall, ~16% of patients experienced at least one event of **peripheral neuropathy** (PN) during treatment, yet only a minority of patients had severe PN (5/504, 1%) and all events resolved with entrectinib dose reduction/interruption.

Dysaesthesia was a common (29%) neurologic AE with entrectinib, and the actual impact of entrectinib on sensory perceptions was further highlighted by the high rates of dysgeusia (42%) observed in the safety population. Nearly all reported cases were mild to moderate in severity and were generally manageable without entrectinib interruption/dose reduction.

The incidence of **ataxia** was approximately 16% (Grade ≥3 0.8%). All AEs resolved following entrectinib interruption/dose reduction, yet approximately 1/3 of subjects who experienced a fall/near fall AE had also reported a concurrent ataxia-related AE: this is considered or relevance, in particular for subjects at higher risk of fall (e.g. the elderly). The impact of CNS metastasis status on ataxia was investigated, yet in the original safety report only a slight increase in the rate of ataxia-related AEs was observed in subjects with brain metastasis (20.9% vs. 17.1%), further supporting the role of entrectinib in the genesis of ataxia-related AEs.

Approximately 5% of subjects in the safety population had at least one **syncope** event (Grade ≥3 3%). Alternative causes for syncope were identified, however, in a significant portion of the subjects who experienced a syncope event, and in the absence of proper controls the real incidence of entrectinib-related syncope remains uncertain.

Seizure AEs were uncommon during treatment with entrectinib (2.2%, all Grade 1 or 2) and the vast majority of subjects with at least one episode of seizure had CNS metastases or primary brain tumours at baseline. The actual role of entrectinib as a possible "facilitating factor" for seizures in subjects with brain involvement is hardly establishable in the absence of direct controls; nonetheless, from a

conservative perspective, seizure should be included in the adverse drug reactions profile of entrectinib. *Cardiovascular toxicity*

Congestive heart failure (CHF) has been reported across clinical trials with entrectinib. These reactions were observed in patients with or without a history of cardiac disease and resolved upon treatment with diuretics and/or entrectinib dose reduction/interruption. No potential mechanism for entrectinib to elucidate/contribute to congestive heart failure has been identified yet. For patients with symptoms or known risk factors of CHF, left ventricular ejection fraction (LVEF) should be assessed prior to initiation of entrectinib treatment. Patients receiving entrectinib should be carefully monitored and those with clinical signs and symptoms of CHF, including shortness of breath or oedema, should be evaluated and treated as clinically appropriate. Congestive heart failure is addressed in sections 4.2, 4.4 and 4.8 of the SmPC.

QTc interval prolongation has been observed in patients treated with entrectinib in clinical trials. Use of Rozlytrek should be avoided in patients with a baseline QTc interval longer than 450 ms, in patients with congenital long QTc syndrome, and in patients taking medicinal products that are known to prolong the QTc interval. In addition, entrectinib should be avoided in patients with electrolyte imbalances or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias . If in the opinion of the treating physician, the potential benefits of entrectinib in a patient with any of these conditions outweigh the potential risks, additional monitoring should be performed and a specialist consultation should be considered.

Assessment of ECG and electrolytes at baseline and after 1 month of treatment with entrectinib are recommended. Periodic monitoring of ECGs and electrolytes as clinically indicated throughout entrectinib treatment, are also recommended. Based on the severity of QTc prolongation, entrectinib treatment should be modified (see sections 4.2 and 4.4 of the SmPC).

Lung toxicity

Pneumonitis (also including interstitial lung disease, alveolitis and radiation pneumonitis) was observed in 2.% of patients were reported in the entrectinib safety population. Further **pleural effusion** AEs were also not uncommon (8.2%, grade ≥3 3.1% in the original safetyreport) and were observed in all safety subsets with the exception of the paediatric subgroup. The evaluation of actual role of entrectinib exposure in promoting pleural effusion is uncertain, since causality assessment is complicated by lack of direct controls and presence of confounders (e.g. lung metastasis), yet cannot be excluded, considering that a similar rate of pleural effusion AEs has been observed in all patients, irrespective of cancer type. Further, fluid retention-related AEs are reported as "very common" with entrectinib. From a conservative perspective the role of entrectinib in the onset of pleural effusion cannot be definitively ruled out.

Gastrointestinal toxicity

GI toxicity was not negligible, with a significant fraction of subjects in the initial safety report experiencing constipation (45.9%), diarrhoea (34.6%), nausea (34.4%) and vomiting (24.2%). Severe (Grade ≥3) GI AEs were observed, however, only in a minority of subjects (5.4%), the most common being diarrhoea (2%), abdominal pain and constipation (0.6% each).

Myelotoxicity

Non-cytotoxic **myelotoxicity** is a known toxicity of most TKIs, and entrectinib is no exception. Most changes in hematologic parameters were of limited clinical relevance (i.e. shifts from baseline to Grade 1 or 2); hematologic toxicity was transitory in nature and overall manageable with standard supportive procedures.

Eye disorder

Eye disorder events were reported in 26% of patients. Vision blurred (including the PTs of diplopia, vision blurred and visual impairment) has been included in section 4.8 of the SmPC.

Bone fractures

Fractures were experienced by 5.3% (25/475) of adult patients. In general, there was inadequate assessment for tumour involvement at the site of fracture; however, radiologic abnormalities possibly indicative of tumour involvement were reported in some adult patients. Most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft). No patients discontinued entrectinib due to fractures.

In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area. The median time to fracture was 3.4 months (range: 0.26 months to 18.5 months) in adults. Entrectinib was interrupted in 36.0% of adults that experienced fractures.

Laboratory and vital signs abnormalities

A significant fraction of subjects in the entrectinib safety database (~40%) experienced at least one renal AE, the more frequent PT being **blood creatinine increased** (25.4%). Based on the available data, inhibition of Trk receptors can result in urinary retention, which might contribute to the high risk (13.8%) of urinary tract infection.

Abnormal liver function tests were not uncommon in subjects treated with entrectinib (22.6%), with the majority of events characterised by an increase in transaminases (AST increased 17.5%, ALT increased 16.1%). Reassuringly, no AE of hepatic drug injury was reported yet. Overall, the available data do not suggest that direct disease involvement of the liver is the main driver of the observed hepatic toxicity, in particular with respect to transaminase increases.

Abnormalities in vital signs were observed in subjects exposed to entrectinib, in particular 6 patients in study STARTRK-NG experienced a **decrease in heart rate** >20 beats per minute from baseline, 15.8% of patients in the overall safety population had at least 1 AE of **hypotension** and 4.5% experienced **hypertension**.

Hyperuricemia has been observed in patients treated with entrectinib. Serum uric acid levels should be assessed prior to initiating Rozlytrek and periodically during treatment. Patients should be monitored for signs and symptoms of hyperuricemia. Treatment with urate-lowering medications should be initiated as clinically indicated and Rozlytrek withheld for signs and symptoms of hyperuricemia. Rozlytrek dose should be modified based on severity (see sections 4.2, 4.4 and 4.8 of the SmPC).

Changes in weight

Weight increase due to deregulated food intake was considered a consequence of TRK inhibition by entrectinib. Overall, 70.8% of patients experienced a ≥5% weight increase during treatment, and 101 subjects with a normal BMI at baseline were subsequently classified post-treatment as overweight or obese. Taking into account that most patients did not report a concurrent event of fluid retention, the pharmacodynamic effect of entrectinib through TrkB inhibition may provide a plausible mechanism for weight increase.

Safety in special populations

The overall safety profile of entrectinib in the elderly patients is similar to the safety profile observed in patients younger than 65 years of age. Adverse reactions occurring more frequently in the elderly compared to patients less than 65 years old were dizziness (48.5% vs 36.6%), blood creatinine increased (31.5% vs 23.3%), and hypotension (21.5% vs 14.7%), ataxia (23.8% vs 12.8%).

Incidence of AEs was generally similar in patients with and without CNS metastases at baseline, except for a higher frequency of serious AEs and grade ≥3 AEs in patients with baseline CNS metastasis. Cognitive disorder events were generally reported at a higher frequency in patients with baseline CNS metastasis compared to those without CNS metastasis at baseline. This is reflected in section 4.8 of the SmPC.

Female patients of childbearing potential should have medically supervised pregnancy testing prior to initiating entrectinib therapy. Entrectinib is not recommended during pregnancy and in women of childbearing potential not using contraception. Female patients receiving entrectinib should be advised of the potential harm to the foetus. Female patients should be advised to contact the doctor, should pregnancy occur. It is unknown whether entrectinib or its metabolites are excreted in human milk. A risk to the breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with Rozlytrek (see discussion on non-clinical aspects).

Entrectinib has moderate influence on the ability to drive and use machines. Patients should be instructed not to drive or use machines until the symptoms resolve, if they experience cognitive adverse reactions, syncope, blurred vision, or dizziness, during treatment with entrectinib (see sections 4.4, 4.7 and 4.8 of the SmPC).

Supportive safety data and post-marketing experience

Information from the supportive safety data sources was limited, yet overall in line with data from the integrated safety database.

Assessment of paediatric data on clinical safety

The safety of entrectinib in paediatric patients was established based on extrapolation of data from three open-label, single-arm clinical trials in adult patients with solid tumours harbouring an *NTRK* gene fusion (ALKA, STARTRK-1 and STARTRK-2), and data from 32 paediatric patients (30 patients enrolled in STARTRK-NG, and 2 patients enrolled in STARTRK-2). Of these, 2 patients were less than 2 years old, 23 patients were 2 to 11 years old, 7 patients were 12 to 17 years old.

The fraction of patients harbouring on-target gene fusions is 17/32, yet only 14 out of 17 (9 with NTRK 1/2/3 gene fusions and 5 with genetic alterations involving ROS1) are representative of the claimed indication.

The median exposure in the paediatric safety population is 5.6 months (11.7 months when only on-target patients are considered), which allows for a more reliable characterisation of the entrectinib safety profile. On the other hand, nearly half of the patients included in the paediatric dataset (15/32, most with clinically advanced neuroblastoma) had no detectable relevant gene fusion (i.e. off-target population) and their contribution to the safety analysis is limited (median exposure 1.8 months).

The rates of paediatric patients who experienced at least one treatment-emergent AE (100%), SAE (43.8%) and severe AE (Grade ≥3 AE, 65.6%) are overall in line with what was observed in the adult population (SAE rate ~40% and Grade ≥3 AE rate ~60%) with a similar drug exposure [5.5 months]. No Grade 5 AEs have been reported in the enrolled paediatric population.

The median dose intensity was high (96.3%), with rates of AEs leading to discontinuation, dose reduction or interruption (9.4%, 34.4% and 46.9%, respectively) also in line with those reported in the overall safety population (i.e. 9%, 26% and 46%, respectively). Weight increased (4 patients) and blood creatinine increased (2 patients), were the most common AEs which led to dose reduction and neutrophil count decreased (3 patients), diarrhoea (3 patients) and pyrexia (3 patients) to dose interruption, respectively.

A full characterization of the safety profile of entrectinib in paediatric patients is problematic, mainly because of reduced sample size. The AEs reported in children/adolescents appear to be in line with the entrectinib safety profile observed in adults, although some differences can be noted. Compared to adult patients, paediatric patients were more likely to experience e.g. nausea (30.9% vs. 46.9%), pyrexia (18.3% vs.56.3%), weight increase (25.3% vs. 50%), pain in extremity (9.1% vs. 40.6%), cough (20.2% vs. 50%), decreased appetite (10.9% vs. 31.3%), anaemia (26.3% vs. 59.4%) and neutropenia (11.3% vs. 40.6%). Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increased incidence) in paediatric patients compared to adult patients were neutropenia (28.1% vs. 3.4%), weight increased (21.9% vs 6.9%), headache (6.3% vs 0.6%) and bone fractures (12.5% vs 1.9%).

Younger patients were also more prone than adults to haematological (68.8% vs. 37%, respectively), liver (71.9% vs. 22.6%), renal (68.8% vs. 40.5%) and ocular toxicity (46.9% vs. 26%), and more likely to experience bone fractures (21.9% vs. 5.3%). Bone fractures were reported in patients less than 12 years of age and were localised in the lower extremity (with a predilection for hip, femur and tibia). Bone fractures in paediatric patients generally occurred with minimal or no trauma. Three patients had more than one occurrence of a fracture and 3 patients had entrectinib treatment interrupted due to a fracture. All patients continued entrectinib treatment and all but one event of fracture recovered. In 2 paediatric patients, bilateral femoral neck fractures occurred.

For the majority of patients, concurrent risk factors for development of fractures (e.g. steroid use, radiation, stem cell transplantation, low grade hypocalcaemia, reduced vitamin D levels and osteopenia) were also reported. Nonetheless, a direct role of entrectinib in the genesis of bone fracture cannot be excluded, due to the discussed potential impact of TRK/ROS1 inhibition in physiological bine remodelling processes. The STARTRK-NG study has been modified to collect blood markers of bone metabolism and reabsorption, and regularly scheduled DXA scans and hand and knee x-rays have been implemented to further investigate the role of entrectinib in bone fractures. Patients with signs or symptoms of fractures (e.g., pain, abnormal gait, changes in mobility, deformity) should be evaluated promptly (see sections 4.4 and 4.8 of the SmPC).

On the other hand, the incidence of cognitive AEs was still lower in paediatric patients compared to adults (9.4% vs. ~24%, respectively).

Safety analyses stratified by paediatric age class were also provided to further characterize the tolerability of entrectinib in the target population, which includes patients aged ≥12 and <18 years: although some differences could be observed in the safety profile of children and adolescents (e.g. a higher incidence of diarrhoea [47.8% vs. 0], vomiting [43.5% vs. 0], white blood cell count decreased and decreased appetite [39.1% vs 14.3%], dehydration [30.4% vs 0], hypophosphatemia [30.4% vs 0] hypalbuminaemia [26.1% vs 0], urinary tract infections [26.1% vs 0%], and pollakiuria, proteinuria, pruritus, somnolence, urinary incontinence [21.7% vs 0%, each]), poor numbers question the reliability of any possible inference. Interestingly, it is noted that no event of bone fracture was reported in patients aged ≥12 years: this is in line with previous data showing a lower risk for bone fractures in adults compared to children, yet due to the limited dataset no definitive conclusion can be drawn.

Overall, the available safety data in the paediatric setting are limited, since only 32 subjects who received entrectinib were aged <18 years. Most importantly, only 14/32 paediatric patients had tumours with NTRK 1/2/3 or ROS1 gene fusions, and 7/32 were aged ≥12 and <18 years, as per the claimed indication. The longer median exposure (5.6 months, up to 11.7 months for "on-target" subjects) in the updated analysis allowed, however, for a better characterisation of entrectinib toxicity in younger patients. In this regard, despite some uncertainty due to poor numbers, lack of direct controls and clinical heterogeneity, the paediatric safety profile of entrectinib appears to be overall in

line with that observed in adults. Some differences (e.g. a higher incidence of haematological, liver, renal and ocular toxicity, and a greater risk of bone fractures and weight increase) can, however, be noted.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

In order to further characterize the safety profile of entrectinib in patients aged ≥12 and <18 years, additional safety data should be provided post-approval. The Applicant will submit a safety report in all entrectinib-treated adolescent patients from STARTRK-NG (CO40778) and any other study with entrectinib where adolescent patients are enrolled post-approval, by the end of 2023. The report will include (but not limited to) assessment on growth and development and important risks such as , bone fractures, neurocognitive disorders, CHF and QT interval prolongation (see SOB).

2.6.2. Conclusions on the clinical safety

Overall, the safety database in the claimed indications is of limited extent, yet acceptable in the context of such rare conditions. Based on available data, the safety profile of entrectinib is considered overall manageable. There are limited safety data in adolescents, however, the safety profile in adolescents is similar to the overall safety profile of Rozlytrek. Adverse reactions Grade ≥3 reported in adolescents were neutropenia and headache.

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

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. (see SOB).

2.7. Risk Management Plan

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	• Use in Patients with Hepatic Impairment • Safety in long term use

Pharmacovigilance plan

Neither category 1 nor 2 studies.

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

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
2] and CO40778 [STARTRK-NG] studies (PAESs)				

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

Risk minimisation measures

Safety concern	Risk minimization measures
Fractures	**Routine risk minimization measures:** SmPC Sections , 4.4 (Fractures) and Section 4.8 (undesirable effects) of the SmPC provide recommendations on risk management approach **Additional risk minimization measures:** None
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
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
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 recommendations on risk management approach if neurocognitive changes development. **Additional risk minimization measures:** None

Safety concern	Risk minimization measures
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
Use in Patients with Hepatic Impairment	**Routine risk minimization measures:** None **Additional risk minimization measures:** None
Safety in long term use	**Routine risk minimization measures:** None **Additional risk minimization measures:** None

Conclusion

The CHMP and PRAC considered that the risk management plan version 2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 18.06.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of entrectinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers entrectinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets 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.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rozlytrek (entrectinib) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under a conditional marketing authorisation [REG Art 14-a].

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indications for entrectinib are:

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older, with solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and

- who have not received a prior NTRK inhibitor

- who have no satisfactory treatment options (see sections 4.4 and 5.1).

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.

ROS1 positive advanced NSCLC

The ROS proto-oncogene 1 (ROS1) encodes an orphan receptor tyrosine kinase. ROS1 gene rearrangements from chromosomal translocations lead to constitutive activation of the ROS1 kinase that drives cellular transformation and promotes survival and proliferation through downstream signalling. ROS1 rearranged NSCLC has been described as a distinct molecular type in approximately 1–2% of patients with NSCLC, usually non-overlapping with other main molecular alterations. Incidence of brain metastases ranges from 20-50%. FISH has been the standard approach to detecting ROS1 rearrangements. NGS is an emerging technology. Similarly to what observed for NSCLC ALK-positive patients, ROS-1 positive NSCLC patients are typically young, female, non-smokers and with adenocarcinoma histology.

NTRK fusion positive solid tumours

NTRK gene fusions have been identified at low frequencies in a wide range of commonly occurring tumours, such as lung cancer, breast cancer, colorectal cancer, thyroid cancer, sarcoma and others. In very rare tumours, such as infantile fibrosarcoma (IFS), secretory/juvenile breast cancer, and mammary analogue secretory cancer of the salivary glands (MASC), however, NTRK gene fusions are the defining genetic feature occurring in most or all cases.

The purpose of treatment in this disease setting is to reduce symptoms of disease, and to prolong survival. It is not excluded that patients with locally advanced disease might become operable and potentially cured, however.

The additional indication "or where surgical resection is likely to result in severe morbidity" concern patients who have a life-threatening malignant disease although presently in a potentially curable stage. They are presently surgically curable but at the cost of mutilating surgery affecting function of body parts. The prognostic significance of NTRK fusion and its influence on a tumour's sensitivity to classical treatments is not known for the time being.

3.1.2. Available therapies and unmet medical need

ROS1 positive advanced NSCLC

Crizotinib is currently approved in the EU for the treatment of adult patients with ROS1-positive advanced NSCLC. Crizotinib approval was based on 53 subjects included in the single arm trial PROFILE-1001. Recently published updated results of this study showed that, after a median FU of 62.6 months, ORR was 72% (95%CI 58, 83; CR 11%), median DOR 24.7 months (95%CI 15.2, 45.3), median PFS 19.3 months (95%CI 15.2, 39.1), median OS 51.4 months (95% CI, 29.3, NR; probabilities of survival at 6, 12, 24, 36, and 48 months of 91%, 79%, 67%, 53%, and 51%, respectively).

NTRK fusion positive solid tumours

A Conditional Marketing Authorisation was granted by the European Commission on 19/09/2019 to Vitrakvi (larotrectinib), an NTRK inhibitor, for the treatment of adult and paediatric patients with solid tumours that display 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 no satisfactory treatment options.

3.1.3. Main clinical studies

ROS1 positive advanced NSCLC

The initially submitted data supporting the indication for Entrectinib in ROS1 positive NSCLC is represented by an integrated analysis including 53 adult patients with ROS1 positive advanced NSCLC. Subjects were pooled from the three single-arm clinical studies of entrectinib in adult. All patients included in the pooling received at least one dose of entrectinib, had measurable disease at baseline by investigator, had ECOG≤2 and did not receive prior ROS1 inhibitors. Patients in the ROS1 NSCLC analysis had at least 12 months of follow-up from the time of first response. Results of larger dataset including n=94 subjects (at least 12 months of follow up) and n=161 (at least 6 months of follow up) were provided.

NTRK fusion positive solid tumours

The initially submitted data supporting the indication for Entrectinib in NTRK fusion positive solid tumours is represented by 54 adult patients with NTRK fusion-positive solid tumours. Subjects were pooled from the three single-arm clinical studies of entrectinib in adult. All patients included in the pooling received at least one dose of entrectinib, had measurable disease at baseline by investigator, had ECOG≤2 and did not receive prior NTRK inhibitors. Patients in the NTRK analysis had at least 6 months of follow-up. A larger dataset including n=74 subjects with >6 months of follow up was provided.

Patients NTRK fusion positive solid tumours from the paediatric study STARTRK-NG, and patients within the compassionate use of entrectinib, have been presented separately as supportive for the NTRK indication in the paediatric age.

3.2. Favourable effects

ROS1 positive advanced NSCLC

In 94 patients (at least 12 months of follow up) ORR was 73.4% (63.3, 82.0) (CR 11.7%) and mDOR was 16.5 months (14.6, 28.6). In the dataset including 161 patients (at least 6 months of follow up) ORR was 67.1% (95%CI 59.3;74.3) and median DoR is 15.7 months (95%CI 13.9;28.6).

In 34 patients with CNS disease at baseline, IC-ORR was 50% (95%CI 32.4%, 67.6%), and median IC-DOR 12.9 months (95%CI 5.6, 22.1). Of those, in 22 patients receiving no brain RT or RT>2 months before, IC-ORR was 36.4% (95%CI 17.2%, 59.3%).

NTRK fusion positive solid tumours

In the NTRK evaluable analysis set (n=74), ORR by BICR per RECIST 1.1 (confirmed) was 63.5% (95%CI 51.5, 74.4), with 5 (6.8%) CRs (CR in 2 patients with breast secretory tumour, 2 with MASC and 1 with NSCLC). Median DOR was 12.9 (95%CI 9.3, NE). In rare tumours with high prevalence (>90%) of NTRK fusions, i.e. breast secretory cancer and salivary MASC, ORR was >90%.

In patients with brain metastases confirmed by BICR (n=11), IC-ORR was 54.5% (95%CI 23.38, 83.25). Median IC-DOR was not estimable. Among them, 8 subjects not previously irradiated or with brain RT >2 months had an IC-ORR of 62.5% (95%CI 24.5%, 91.5%).

Of the 6 paediatric patients having NTRK fusion-positive solid tumours evaluated for efficacy, all achieved an objective response by BICR (2 CR and 3 PR plus 1 PR not yet confirmed at the CCOD).

3.3. Uncertainties and limitations about favourable effects

ROS1 positive advanced NSCLC

Data on intracranial activity are limited and uncontrolled. No data on intracranial activity of established therapies in ROS-1 are available. In view of the high prevalence of CNS metastasis in NSCLC cancer, a PAES will be conducted to provide further data in patients with baseline CNS disease (see Annex II).

NTRK fusion positive solid tumours

Due to the limited efficacy data base, the extent to which tissue of tumour origin or concomitant genetic alterations impact efficacy is in need of further clarification.

Due to the small sample size, the confidence intervals are generally wide, making efficacy estimates generally imprecise and hampering the possibility to draw conclusions regarding efficacy in subgroups, e.g. with regard to age groups and gene fusion type. This aspect will be addressed by the post-marketing study (see SOB and RMP).

In light of the claimed site and histology independent indication, the non-clinical pharmacological data-package is considered insufficient to extrapolate activity in all clinical TRK fusions and tumour histologies including paediatric tumours.

Applicable to both indications

Data were pooled and derived from single arm studies which render interpretation of time-to-event endpoints limited.

The pooled analyses contained a mix of data intended as pivotal or not. A fundamental problem in basing decisions from data pooled over almost the whole study program is that the confirmatory element is obliterated. The risk of incorrectly concluding efficacy is much larger if these conclusions are based on analyses made in a single step rather than on a sequence of studies.

Intracranial activity evaluated in a limited number of subjects. In IC responders who received RT within 2 months, an effect of the recent RT to the CNS response cannot be excluded, making difficult to determine the real contribution of entrectinib to the observed IC-ORR. Therefore, the group "No brain RT or brain RT >2 months" is considered to better estimate the IC-response.

3.4. Unfavourable effects

The provided safety database is comprised of 504 subjects who received at least one dose of entrectinib across four clinical studies. Four distinct safety analysis subsets were identified by the Applicant based on type of genetic/molecular alteration (NTRK fusion positive subjects n=113, ROS1 positive patients with NSCLC n=210, subjects outside the claimed indication [i.e. with ROS1 positive non-NSCLC, ALK fusion positive solid tumours or with no gene fusion] n=152) and age (paediatric subjects n=32) (data cut-off date 31 October 2018 for the overall population and 1 November 2019 for paediatric subjects).

The most frequently reported TEAE by SOC were "Nervous System Disorder" (82.5%), "Gastrointestinal" (81.5%), "General Disorders and Site Conditions" (73.4%), "Respiratory, Thoracic and Mediastinal Disorders" (~60%), "Musculoskeletal and Connective Tissue Disorders" and "Investigations" (~55%) and "Infections and Infestations" SOCs.

The most frequently reported (≥25% of patients) AEs by PT were fatigue (45%), constipation (43%), dysgeusia (42%), dizziness (36%), diarrhoea (34%), nausea (32%), anaemia (28%), peripheral oedema (27.8%), dyspnoea (27%), weight increased (26%) and blood creatinine increased (25%). The majority of the reported AEs were Grade ≤2. The most common Grade 3/4 AEs (≥ 2% of patients) were anaemia (9.7%), weight increased (7.3%), dyspnoea (5.4%), fatigue (4.8%), pneumonia (3.8%), AST increased (3.6%), ALT increased (3.4%), syncope (3.0%), pulmonary embolism, pleural effusion and neutrophil count decreased (2.8% each), urinary tract infection and diarrhoea (2.6% each), hypoxia (2.4%) and hypophosphatemia (2.2%).

The most commonly reported SAEs by PT were pneumonia (3.9%), dyspnoea (3.7%), pleural effusion (3.4%), pulmonary embolism (2.3%) and pyrexia (2%).

3.5. Uncertainties and limitations about unfavourable effects

Overall, the safety database in the claimed indications is relatively limited, although acceptable in the context of the rare biomarker positive indications. In addition, the uncontrolled design of all the studies does not allow to clearly disentangle signs/symptoms of the underlying malignancy and entrectinib-related adverse events.

The integrated safety population is also characterised by a significant heterogeneity in terms of age (min 4 months, max 88 years), type of underlying malignancy, dose administered (from 100 to 1600 mg/m2/day, BSA-based vs. flat dose), drug regimen (4 days on/3 days off for 21 days in 28-day cycles vs. continuous daily dosing) and formulation (F1, F2A and F2B). Such significant heterogeneity in an uncontrolled setting limiting precise evaluations of entrectinib safety profile and the reliability of causality relationships.

The paediatric safety database is very limited (32 patients, 7 aged ≥12 and <18 years). This is further complicated by high rate of "off-target" patients (15/32), heterogeneity of the underlying tumours and different doses received. The significant limits in the paediatric safety dataset, especially in adolescents, do not allow a full characterisation of the safety profile of entrectinib in this setting. Additional data need to be collected post approval (see SOB).

3.6. Effects Table

Table 99: Effects Table for entrectinib in NTRK fusion positive solid tumors and in ROS1 positive NSCLC

Effect	Short Description	Unit	Treatment	Uncertainties/ Strength of evidence
Favourable Effects				
Indication: patients with **ROS1-positive**, **advanced NSCLC (n=94) (CCOD 1 May 2019)**				
ORR	Objective response rate (confirmed) per RECIST 1.1 by BICR	% 95%CI	73.4% (63.3, 82.0)	Post-hoc definition of the SAP
DOR	Duration of response per RECIST 1.1 by BICR	Median (months) 95%CI	16.5 (14.6, 28.6)	Half of the patients still on treatment at the CCOD.
IC-ORR	Intracranial objective response rate (confirmed) per RECIST 1.1 by BICR	% 95%CI	50.0% (32.4, 67.6)	Evaluated in 34 subjects with baseline CNS disease by BICR.
IC-DOR	Intracranial duration of response per RECIST 1.1 by BICR	Median (months) 95%CI	12.9 (5.6, 22.1)	Evaluated in 34 subjects with baseline CNS disease by BICR.
Indication: adult and paediatric patients with **NTRK fusion-positive** locally advanced or metastatic solid tumours, who have progressed following prior therapies or as initial therapy when there are no acceptable standard therapies. **Pooled study population (n=74) (CCOD 31 October 2018)**				
ORR	Objective response rate (confirmed) per RECIST 1.1 by BICR	% 95%CI	63.5% (51.5, 74.4)	Different ORR across tumor types. Primary CNS tumors not included.
DOR	Duration of response per RECIST 1.1 by BICR	Median (months) 95%CI	12.9 (7.9, NE)	31% of patients on treatment at the cut-off date.
IC-ORR	Intracranial objective response rate (confirmed) per RECIST 1.1 by BICR	% 95%CI	54.5% (23.4, 83.3)	Evaluated in 11 subjects with baseline CNS disease by BICR.
IC-DOR	Intracranial duration of response per RECIST 1.1 by BICR	Median (months) 95%CI	NE (5, NE)	Evaluated in 11 subjects with baseline CNS disease by BICR.
Unfavourable Effects (CCOD 31 October 2018)				
Safety population **(n=504) -**				

Effect Short Description	Unit	Treatment	Uncertainties/ Strength of evidence
total AE AE grade ≥3 SAE AE leading to discontinuation AE leading to death	%	99 61.1 39.9 9.1 4.8	Interpretation of safety hampered by: - Single arm study - differences across the safety subsets in exposure, dose, administration regimen, formulation, underlying malignancy, genetics and sample size Highest uncertainty in the paediatric subset. Only 2 grade 5 events assessed as related to entrectinib by investigator, all occurred in adults.
AEs most commonly reported by SOC - Nervous System Disorder - Gastrointestinal - General Disorders and Site Conditions - Respiratory,Thoracic and Mediastinal Disorders - Musculoskeletal and Connective Tissue Disorders and Investigations	%	 82.5 81.5 73.4 ~60 ~55	
Grade 3-4 AEs most commonly reported by PT (≥5% of patients) - Anaemia - Weight increased - Dyspnoea - Fatigue	%	 9.7% 7.3% 5.4% ~5%	
SAEs most commonly reported by SOC (≥5% of patients) - respiratory thoracic and mediastinal disorders - infections and infestations - nervous system disorders	%	 11.9% 11% 8.5%	
AEs of special interest (AEOSI)			
Neurologic toxicity (≥10% of patients) - dysgeusia - dizziness - parestesia - headache - muscular weakness	%	 42.3 36.1 19.8 17.5 12.3	
Increased creatinine and other renal AEs Hematologic AEs Eye disorders AEs Weight increased Abnormal liver function test and liver dysfunction AEs Congestive heart failure AEs Pneumonitis AEs ECG QT prolonged AEs	%	40.5 37.1 26 26.4 22.6 3.2 2 2	

Abbreviations: NTRK: neurotrophic tyrosine receptor kinase; NSCLC: non-small cell lung cancer; ROS1: proto-oncogene tyrosine-protein kinase 1; ORR: objective response rate; DOR: duration of response; PFS: progression free survival; OS: overall survival; IC: intracranial; BICR: blinded independent central review; CNS: central nervous system; NE: not evaluable; N/A: not available; RECIST: Response Evaluation Criteria in Solid Tumors; CI: confidence interval; AE: adverse event; AEOSI: AE of special interest; PT: preferred term; SOC: system organ class; ECG: electrocardiogram

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

ROS1 positive advanced NSCLC

Entrectinib showed antitumor activity by inducing a relevant objective response rate in ROS1-inhibitor naïve ROS1 positive advanced NSCLC adult patients, of some durability, confirmed with longer follow-up and in larger dataset. The magnitude of this effect is such that it is likely to result in clinically relevant effects on PFS, although uncertainties are still present due to lack of direct controls, whereby an impact of entrectinib treatment on PFS/OS cannot be directly ascertained. The achievement of intracranial responses also in patients who did not received prior brain RT, suggests activity of entrectinib in CNS metastases, although given the small number of patients, estimates should be interpreted with caution. However, intrinsic limitations of the data are related to the single arm design and pooling of patients across studies.

The safety database in the claimed indication is considered limited, yet acceptable. Based on available data, the toxicity profile of entrectinib in adult patients is considered manageable.

NTRK fusion positive solid tumours

Entrectinib showed antitumor activity by inducing objective responses in adult patients with NTRK fusion positive solid tumours. Although there is uncertainty about the precise magnitude of effect, both due to the study conduct and since the understanding of the extent that tissue of origin is an effect modifier is incomplete; the observed overall ORR of 63.5% is considered outstanding.

Responses appear durable, with median >12 months. However, due to limited number of patients in some tumour types, there is uncertainties regarding DOR estimate per tumour type. Overall, the activity in tumours where NTRK-fusions are present, is such that clinically relevant effects may be anticipated, and entrectinib is thus a reasonable treatment option in patients for whom non-NTRK targeted therapeutic options are either not available or have been exhausted.

The impact of tissue of origin and concomitant genetic alterations are not fully understood and will be addressed in the context of the specific obligations (see below).

The safety database in the claimed indication is still considered limited, but acceptable in the context of a rare condition. Based on available data, the safety profile of entrectinib in adult patients is considered manageable.

Paediatric setting:

An indication in adolescents is considered possible based on allometric scaling (with fixed allometric exponents 0.75 and 1) and leaving the possibility to justify if the difference in bioavailability is not observed in adolescent compared to adults. The model has been updated including only adolescents taking F1 and F2 formulations and testing the covariate F1 on Frel in adolescent population; the relative BA in adolescents is 24% lower than adults and it is not so far different from that observed in the original popPk model including the overall paediatric population (28%). The only aspect that at present can overcome the lower BA observed for F1 formulation in paediatric patients is the presence of the acidulant in F06 formulation that resolved the sensitivity of entrectinib to gastric environment and dosing conditions. This can suggest that the F06 formulation can lead to a similar BA in adolescents and in adults.

The simulations of the exposure (AUCss) of entrectinib and its metabolite, M5 provided by the Applicant showed that, also for lower categories of weight (from 30 kg) included within the BSA 1.1-

1.5 m2, the exposure in subjects aged ≥12 years is within those obtained in adults. The applicant claimed that the proposed posology of 300 mg/m2, i.e. 400 mg in the BSA group ≥1.1 to <1.5 m2, is safer as the risk for over-exposure is lower compared to the FDA approved posology of 500 mg to this BSA group. The Applicant proposed to maintain the 400 mg dose for category IV for a more conservative approach and to minimise the risk of over-exposure, and it is agreed.

The low number of adolescents in the age group 12-18 years with tumours harbouring NTRK 1/2/3 gene fusions is acknowledged. Indeed, since the start of the expansion portion of STARTRK-NG in Dec 2017 and up to now, out of the 14 paediatric patients recruited with a NTRK gene fusion there was only one patient ≥12 years of age. It is also noted that, out of 28 paediatric patients treated with the approved NTRK inhibitor larotrectinib, 3 only were aged 12-18 years (EPAR Vitrakvi). Based on the current recruitment benchmark, the number of patients ≥12 years that the Applicant expect to enroll within in the SOB1 may not be higher than 3 - 5 patients (target date 31 March 2027).

In conclusion, the CHMP is of the opinion that an indication for entrectinib for 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, can be granted **in adolescents (≥ 12 years)**. The dose recommendation in children is based on data from popPK analysis which is considered acceptable based on the simulation provided. The activity of entrectinib in adolescents is considered established based on extrapolation of data obtained in adult patients with NTRK fusion positive solid tumours.

A full characterisation of the safety profile of entrectinib in paediatric patients remains problematic, mainly because of the limited exposure, the reduced sample size and the high heterogeneity and lack of controlled data. Overall, the safety profile in paediatric patients is in line with what was observed in adults. Additional safety data in adolescent will be provided as part of the SOB.

Even though the safety data in patients 12-18 years of age is scarce, considering the life-threatening nature of the disease and that entrectinib should only be used when there are no satisfactory treatment options (i.e., for which clinical benefit has not been established, or where such treatment options have been exhausted), The benefit risk is considered positive in this patient population.

3.7.2. Balance of benefits and risks

ROS1 positive advanced NSCLC

The ORR and DoR are similar to what was seen with crizotinib (Xalkori), and deemed outstanding and clinically meaningful; i.e. very likely to translate into a clinically relevant PFS effect. The safety profile does not raise concerns that this benefit would be offset by toxicity in the relevant treatment setting. The balance of benefits and risks can be established as positive based on the outstanding activity and a reasonable characterisation of the safety profile. While preliminary data indicating clinically relevant activity are available, the extent of benefit in the important subgroup of patients with brain metastases is not clarified. Therefore, a PAES to address the latter issue, as well as to generate some comparative safety data, in accordance with the Commission Delegated Regulation (EU) No 357/2014 indent c), is mandated.

NTRK fusion positive solid tumours

The overall activity in NTRK-positive tumours is deemed clinically meaningful in a setting where non-targeted therapies are either not established, or where such treatment options have been exhausted. The extent to which tissue of origin and concomitant genetic alterations are effect modifiers, is not completely understood. Data are not deemed comprehensive and need further exploration through post authorisation measures. The benefit is not offset by the emerging safety profile.

The dose recommendation in children is based on data from popPK analysis. In light of the updated popPK model and considering all the simulations provided, an indication has been considered possible to be granted in adolescents (≥ 12 years).

3.7.3. Additional considerations on the benefit-risk balance

ROS1 NSCLC indication: A PAES to address the activity of entrectinib in patients with CNS disease (in accordance with the Commission Delegated Regulation (EU) No 357/2014 indent c)), has been imposed by the CHMP. The proposed study is an open-label randomized 1:1 RCT of entrectinib vs crizotinib in 1L (i.e. TKI naïve and no prior systemic therapy) in ROS1 NSCLC patients with and without brain metastases at baseline (both measurable and non-measurable). Based on the rate of accrual observed to date, the Applicant plans to enrol 220 patients, of whom at least 30% (66 pts, i.e. 33 per arm) will be ensured to have baseline CNS metastases. Patients will be stratified by brain metastases (no CNS/measurable CNS/non-measurable CNS disease) and prior brain RT <2 months (yes/no). The primary endpoint is PFS per RECIST 1.1 by IRC in the subpopulation with CNS metastases at baseline. A total of 49 PFS events in 56 months after first patient in are expected, assuming PFS 8 vs 14 months (HR 0.57). The minimum detectable difference (MDD) would be HR=0.692, corresponding to a gain of 3.6 months in median PFS. A two-sided alpha of 20%, and power 75% have been used. CNS-PFS in the entire population is a secondary endpoint. The targeted filing of the clinical study report is in 2027.

The target population and the sample size calculation based on the assumptions made by the Applicant appear overall reasonable. It is acknowledged that the available data for crizotinib are extremely limited to make precise assumption of PFS in patients with brain metastases.

The minimum detectable difference in median PFS (3.6 month of improvement) could be considered of some relevance in patients with brain metastases at baseline, although effect on other time related endpoint such as PFS2 and OS should be continued to be collected to ensure no late detrimental effect. PFS in the overall ITT population will be collected, together with data on the first site of recurrence in both populations.

The Applicant selected a "relaxed" alpha of 20% for the primary endpoint (and a power of 75%), justified in order to allow the study to be completed within a reasonable timeframe, in keeping with estimated recruitment of 1.2 CNS efficacy evaluable patients per month.

Quality aspects:

During the procedure the Applicant informed the CHMP that the proposed drug substance manufacturer failed to reproduce the desired active substance Form A due to unexpected events and that the manufacturing site is not capable of further sourcing Form A. The Applicant has decided to change the active substance polymorphic form for the product and to use the Form C polymorph, and to modify the final manufacturing step of the active substance in order to assure that the desired polymorph is consistently produced. Based on the extensive characterisation studies, a detailed assessment was conducted to demonstrate the comparability of entrectinib Form C with entrectinib Form A. It was demonstrated that Form C is comparable to Form A in terms of chemical and physical properties and stability. Forms A and C were further compared in a clinical bioequivalence study (BE41049) and bioequivalence of Form A and Form C in the finished product was demonstrated.

Based on the demonstrated bioequivalence between finished products formulated with Form A and Form C and the physico-chemical comparability of the active substance of these two polymorphic forms, and the unmet medical need of the product, the CHMP has carefully considered and determined that this approach can be accepted. The traceability of the polymorphic form is assured as polymorphic

form testing is part of the active substance specifications, linking this information with finished product batches under GMP requirements.

Conditional marketing authorisation

As comprehensive data on the product are not available for the treatment of patients with tumours that harbour NTRK1/2/3, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product, which aims at the treatment of a life-threatening disease, falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

A plan for specific obligation (SOB1 and SOB2) has been proposed, which is considered acceptable by the CHMP:

Specific Obligation number 1 (SOB-1) by 31 March 2027

> *- 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 Applicant is planning to include 139 additional NTRK fusion positive efficacy evaluable patients (61 already recruited) for a total of about 200 patients in the upcoming years 2020-2026, with March 2027 as deadline for submission (4 years for recruitment, 1 year of follow up and 1 year to analyse data and present the dossier). The projection is based on the observed recruitment in STARTRK-2 study so far (2.85 patients per month). About 30 pediatric patients are planned to be presented within the SOS (i.e. 22-27 patients < 12 years and 3-5 patients aged >=12 years). Interim safety and efficacy analysis will be submitted by end 2023. Efficacy data from the interim analysis should be presented for the overall efficacy-evaluable population as well as by histology/tumor site. Lack of efficacy within a certain tumor type will be defined by the Applicant as less than 4 responders in a group of sequentially enrolled 13 patients (i.e., ORR <30%), which would trigger information to EMA. In order to further characterize the safety profile of entrectinib in patients aged ≥12 and <18 years, additional safety data will be provided post-approval. The Applicant will submit a safety report in all entrectinib-treated adolescent patients from STARTRK-NG (CO40778) and any other study with entrectinib where adolescent patients are enrolled. The report would include (but not limited to) assessment on growth and development and important risks such as bone fractures, neurocognitive disorders, CHF and QT interval prolongation. The safety report will be submitted by the end of 2023, in order to align with the SOB-1 interim timelines.

Specific Obligation number 2 (SOB-2) 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 Applicant will continue collecting plasma for circulating tumour DNA analysis and tumour tissue when medically feasible, and will use NGS to correlate the following with clinical outcomes: NTRK fusion status and partners, concurrent oncogenic driver mutations, and concurrent additional alterations. Biomarker associations may not be statistically powered for correlation analyses given the rarity and diversity of biomarker alterations. Foundation Medicine F1 CDx for tissue samples and Foundation Medicine F1Liquid CDx for ctDNA (the latter platform will complete analytical validation studies in 2021, will be CE marketed and anticipated to conform to IVDR in 2022) in plasma samples will be used to identify genomic alterations at baseline and progression when medically feasible.

It is understood that a percentage of patients won't be identified with the selected assay due to the lack of intronic NTRK3 coverage of FoundationOne CDx. To overcome this issue, an RNA component to FoundationOne CDx would be needed. The Applicant will update the EMA on whether implementation and/or changes of the test would occur in the context of the annual renewal.

- Unmet medical needs will be addressed, as the sought indication for entrectinib is intended for patients with NTRK gene fusion solid tumours in advanced stages with no (further) standard therapies available. Such conditions are generally associated with poor prognosis and limited survival; the main goal of treatment is palliation, with cure rarely achieved. Uncertainties remain on the precise estimates of efficacy and on the activity across tumour types, which will be addressed within the SOB. In the same setting, Vitrakvi (larotrectinib) recently received a conditional marketing approval in EU. According to EMA/CHMP/509951/2006, Rev.1, "for the demonstration of fulfilment of unmet medical needs by a second or subsequent product, the accumulated clinical data and residual uncertainties concerning the effects of an already conditionally authorised medicine(s) should be taken into account. While the specific obligations are not yet fully completed, it is not possible to confirm the full benefit of a conditionally authorised product, therefore another medicinal product could potentially address the same unmet medical needs, 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." Higher ORR has been apparently seen in diseases where NTRK fusion is pathognomonic compared to other solid tumours, and this is observed in the data presented for both entrectinib and larotrectinib. Despite the limitations of cross-study comparison also due to heterogeneity in dataset composition and the small number of subjects representing each tumour types, the available data support the conclusion that both medicines address the unmet medical need to a similar extent.

In the CMA justification, the Applicant discussed the issue of blood brain barrier permeability and the condition of P-gp substrate for entrectinib. The submitted Apical ER model is not soundly validated to substantiate the statement that entrectinib is a weak substate of P-gp as compared to larotrectinib or crizotinib and, moreover, it cannot be concluded that entrectinib is not at all a P-gp substrate as reported in the SmPC. Besides the drug behavior towards the P-gp, what is also to be considered is the level of expression of P-gp which differs from normal brain (high expression) and in malignant primary brain tumors and metastatic tumors to the brain (low expression) suggesting that MDR mechanisms other than P-gp could be involved in their weak response to chemotherapy (Demeule et al., 2011).

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

It is concluded that Rozlytrek has a positive benefit/risk in the intended indication subject to the agreed specific obligations.

3.8. Conclusions

The overall B/R of Rozlytrek is positive.

Divergent positions are appended to this report.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Rozlytrek is not similar to Onivyde, Nexavar, Yondelis, Cometriq, Bavencio, Lutathera, Zejula, Qarziba and Mepact within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix X

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Rozlytrek is favourable in the following indication:

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older, with solid tumours that have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion,

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and

- who have not received a prior *NTRK* inhibitor

- who have no satisfactory treatment options (see sections 4.4 and 5.1).

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.

The CHMP therefore recommends the granting of the conditional marketing authorisation 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).

Other 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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The 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.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of entrectinib in patients with baseline CNS disease, the MAH should conduct and submit the results of a randomised controlled trial versus crizotinib in treatment naïve ROS1 NSCLC patients. The primary endpoint will be PFS in the subgroup of patients with CNS metastases at baseline.	31 December 2027

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Divergent positions to the majority recommendation are appended to this report.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that entrectinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0010/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

DIVERGENT POSITION DATED 28 May 2020

Rozlytrek EMEA/H/C/004936/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Rozlytrek for the following indications:

1) Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older, with solid tumour that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and

- who have not received a prior NTRK inhibitor

- who have no satisfactory treatment options (see section 4.4 and 5.1).

2) 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

The reason for divergent opinion on the NTRK fusion positive solid tumours indication, is the following:

Though it is acknowledged that entrectinib is active in the proposed target population, the overall dataset is considered too limited to conclude that the data represent clinical benefit. Notably, due to the small sample size, also small changes in the size of even the largest cohorts would have large effects on the ORR. This means that, while the safety profile is deemed manageable, there is such an uncertainty on the observed activity that we cannot conclude on a positive B/R and, in the context of the applied CMA, also not whether the available results address the unmet medical need to a similar or greater extent to what is understood for the already conditionally authorised product (as laid down in EMA/CHMP/509951/2006, Rev.1).

CHMP Members expressing a divergent opinion:

Johannes Lodewijk Hillege

Martina Weise

Jan Müller-Berghaus

The reason for divergent opinion on the ROS1-positive, advanced non-small cell lung cancer (NSCLC) indication is the following:

This application is based on a pooled efficacy analysis, composed of the subpopulation of adult patients with ROS1-positive NSCLC treated across three single-arm studies in adult patients with solid tumors (ALKA, STARTRK-1, and STARTRK-2). It is acknowledged that Rozlytrek in this pooled explorative dataset showed antitumour activity by inducing objective responses of some durability. However, the dataset cannot be considered comprehensive as it is small, the analysis exploratory and, in addition, time related endpoints are difficult to interpret because of a lack of comparative data. Furthermore, a major therapeutic advantage over existing therapies, which is required for a conditional marketing authorization, cannot be demonstrated by the current data.

Feasibility of the proposed PAES study comparing entrectinib with crizotinib is questioned once entrectinib is approved and the targeted reporting date of the PAES in 2027 or even later is not acceptable.

CHMP Members expressing a divergent opinion:

Martina Weise

Jan Müller-Berghaus