25 July 2019
EMA/CHMP/469135/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

VITRAKVI

International non-proprietary name: larotrectinib

Procedure No. EMEA/H/C/004919/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

5-FU	Fluorouracil
ADR	adverse drug reaction
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine transaminase
ANC	absolute neutrophil count
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
AST	aspartate transaminase
ATP	adenosine triphosphate
AUC	area under the concentration versus time curve
AUC0-12	AUC from time 0 to time 12 hours
AUC0-24	AUC from time 0 to time 24 hours
AUC0-inf	AUC extrapolated to infinity
AUC0-t	AUC to last measured or measurable concentration
BCRP	breast cancer resistance protein
BCS	biopharmaceutical classification system
BDGF	brain-derived growth factor
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BID	twice daily
CAPOX	capecitabine + oxaliplatin
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum drug concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CSE	Clinical Summary of Efficacy
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EPAR	European Public Assessment Report
ePAS	extended primary analysis set
ePAS	extended primary analysis set
ePAS2	second extended primary analysis set
ESRD	end-stage renal disease
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FOLFOX	folinic acid (leucovorin calcium) + fluorouracil + oxaliplatin
FOLFOXFIRI	folinic acid (leucovorin calcium) + fluorouracil + oxaliplatin + irinotecan
FUOX	fluorouracil and oxaliplatin;
GCP	Good Clinical Practice
GI	gastrointestinal
GIST	gastrointestinal stromal tumour

HDPE	High Density Polyethylene
hERG	human Ether-à-go-go Related Gene
HPLC	High performance liquid chromatography
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IFL	Folinic acid (leucovorin calcium) + fluorouracil + irinotecan
IFS	Infantile fibrosarcoma
INV	Investigator
IRC	Independent Review Committee
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IV	Intravenous
IVA	Ifosfamide, vincristine, and actinomycin
KF	Karl Fischer titration
LDPE	Low density polyethylene
MASC	mammary analogue secretory cancers
MET	mesenchymal-epithelial transition factor
MHRA	Medicines and Healthcare products Regulatory Agency
MPA	Medical Products Agency
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NDA	New Drug Application
NGS	next generation sequencing
NSCLC	non-small cell lung cancer
NT-3	Neurotrophin-3
NTRK	general term for human neurotrophic tyrosine kinase receptor genes or mRNA
OAT	organic anion transporter
OCT	organic cation transporter
ORR	overall response rate
OS	overall survival
PACMP	Post-Approval Change Management Protocol
PAS	primary analysis set
PD	progressive disease
PE	Polyethylene
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PopPK	Population pharmacokinetics
PP	Polypropylene
PR	Partial response
QD	Once daily
QRS	Represents electrical activity generated by ventricular depolarization prior to contraction of the ventricles
QT	QT interval is the time between the start of the Q wave and the end of the T wave
QTc	Corrected QT interval
QTcF	Fridericia's correction formula
RANO	Response Assessment in Neuro Oncology

RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RMP	Risk Management Plan
Rpm	rotations per minute
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Supplemental analysis set
SAS1-IRC	Supplementary Analysis Set with IRC assessment of tumour response
SCE	Summary of Clinical Efficacy
SD	Standard deviation *or* stable disease
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse events
T_{max}	Time taken to reach the maximum concentration
TRK	tropomyosin receptor kinases
ULN	upper limit of normal
US/USA	United States (of America)
USP	United States Pharmacopoeia
UV	Ultraviolet
XELOX	capecitabine + oxaliplatin
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bayer AG submitted on 24 August 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for VITRAKVI, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 2017.

VITRAKVI was designated as an orphan medicinal product:

EU/3/15/1606 (EMA/OD/184/15) on 11 January 2016 in the following condition: Treatment of soft tissue sarcoma.

EU/3/18/1995 (EMA/OD/213/17) on 21 March 2018 in the following condition: Treatment of salivary gland cancer.

EU/3/18/2097 (EMA/OD/116/18) on 19 November 2018 in the following condition: Treatment of glioma.

EU/3/18/2098 (EMA/OD/117/18) on 19 November 2018 in the following condition: Treatment of papillary thyroid cancer.

All the orphan designations granted for larotrectinib were withdrawn on 11 July 2019.

The applicant applied for the following indication: "Vitrakvi is indicated for the treatment of adult and paediatric patients with locally advanced or metastatic solid tumours (excluding primary central nervous system (CNS) tumours) with a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion after prior standard therapy or as initial therapy when there is no adequate treatment option."

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' 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 P/0182/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0182/2018 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

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 larotrectinib 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.

Protocol assistance

The applicant did not seek protocol assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	15 June 2018
Accelerated Assessment procedure was agreed-upon by CHMP on	26 July 2018
The procedure started on	13 September 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 November 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	13 November 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	19 November 2018
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 November 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	11 December 2018
The Procedure changed from Accelerated to normal Timetable after a clarification meeting that took place on	17th December 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 January 2019
Scientific Advisory Group (SAG) on Oncology was convened to address	27 February 2019

questions raised by the CHMP on	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	05 March 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	28 March 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	29 April 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 May 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	29 May 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	04 June 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 June 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	24 June 2019
The CHMP adopted a report on similarity of Vitrakvi with authorised orphan medicinal product(s) on (Appendix 1)	25 July 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to VITRAKVI on	25 July 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indication is for "the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (*NTRK*) gene fusion", therefore it refers to solid tumours independent of tumour type/histology.

This concerns an overall last line indication although early-line treatment is also included in tumour types where there is no available standard therapy, or, even if therapies are recommended, they do not provide a documented and relevantly sized clinical benefit.

2.1.2. Epidemiology

NTRK gene fusions lead to overexpression and constitutive activation of the tropomyosin receptor kinases TRKA, TRKB, and TRKC, which leads to TRK fusion cancer. The first report of an NTRK gene fusion was described in colorectal cancer in 1986 (Martin-Zanca et al. 1989). More recently, with increasing adoption of comprehensive genomic profiling, NTRK gene fusions have been identified in a wide range of commonly occurring tumours, such as lung cancer, breast cancer, colorectal cancer, thyroid cancer, sarcoma and others, though at low frequencies. In very rare tumours, such as infantile fibrosarcoma (IFS), secretory/juvenile breast cancer, and mammary analogue secretory cancer of the salivary glands, NTRK gene fusions are the defining genetic feature of these tumour types occurring in 93% to 100% of tumours (Vaishnavi et al, 2015). The prevalence of NTRK gene fusions in different tumour types are summarized in Table 1 and shows that TRK fusions are rare.

Patients with advanced cancers have a life-threatening condition and represent an area of unmet medical need.

Table 1: Prevalence of NTRK Gene Fusions in published literature

Tumour	Disease Type	Prevalence	Number of fusions/ Sample count	Source
Sarcoma	Sarcoma	1.00%	1/103	Stransky et al, 2014
	Infantile fibrosarcoma	90.90%	10/11	Bourgeois et al, 2000
	Gastrointestinal stromal tumors	3.20%	1/31	Brenca et al, 2016
Non-Small Cell Lung	Lung large cell neuroendocrine cancer	1.70%	1/60	Fernandez-Cuesta et al, 2014
	Lung adenocarcinoma	3.30%	3/91	Vaishnavi et al, 2013
	Lung adenocarcinoma	0.20%	1/513	Stransky et al, 2014
Salivary	Mammary analogue secretory carcinoma of the salivary glands	100%	15/15	Bishop et al, 2013
Thyroid	Papillary thyroid cancer	12.10%	4/33	Bongarzone et al, 1998 Brzezianska et al, 2006
	Papillary thyroid cancer (post radiation)	14.50%	9/62	Leeman-Neill et al, 2014
	Papillary thyroid cancer	2.00%	3/151	Vaishnavi et al, 2013
Primary Central Nervous System	Glioblastoma	1.20%	2/162	Kim et al, 2014
	Astrocytoma	3.10%	3/96	Jones et al, 2013
	Brain low-grade glioma	0.40%	2/461	Stransky et al, 2014
	Non-brainstem high-grade glioma	10.30%	6/58	Wu et al, 2014
	Diffuse intrinsic pontine glioma	3.70%	2/54	Wu et al, 2014
Biliary	Intrahepatic cholangiocarcinoma	3.60%	1/28	Ross et al, 2014
Colorectal	Colorectal cancer	0.70%	2/286	Stransky et al, 2014
Other	Spitz neoplasm nevi	10.70%	8/75	Wiesner et al, 2014
	Secretory breast carcinoma	91.70%	11/12	Tognon et al, 2002
	Congenital mesoblastic nephroma	60.70%	14/28	Argani et al, 2000 Rubin et al, 1998
	Breast invasive carcinoma	0.10%	1/1072	Stransky et al, 2014
	Skin cutaneous melanoma	0.30%	1/374	Stransky et al, 2014
	Head and neck squamous cell carcinoma	0.50%	2/411	Stransky et al, 2014
	Melanoma	0.3%	1/374	Stransky et al, 2014 Wiesner et al, 2014

The prevalence of NTRK fusions in some common tumour types, according to two public databases, is shown below.

Table 2: Frequency of NTRK gene fusion in common types of cancers in public databases

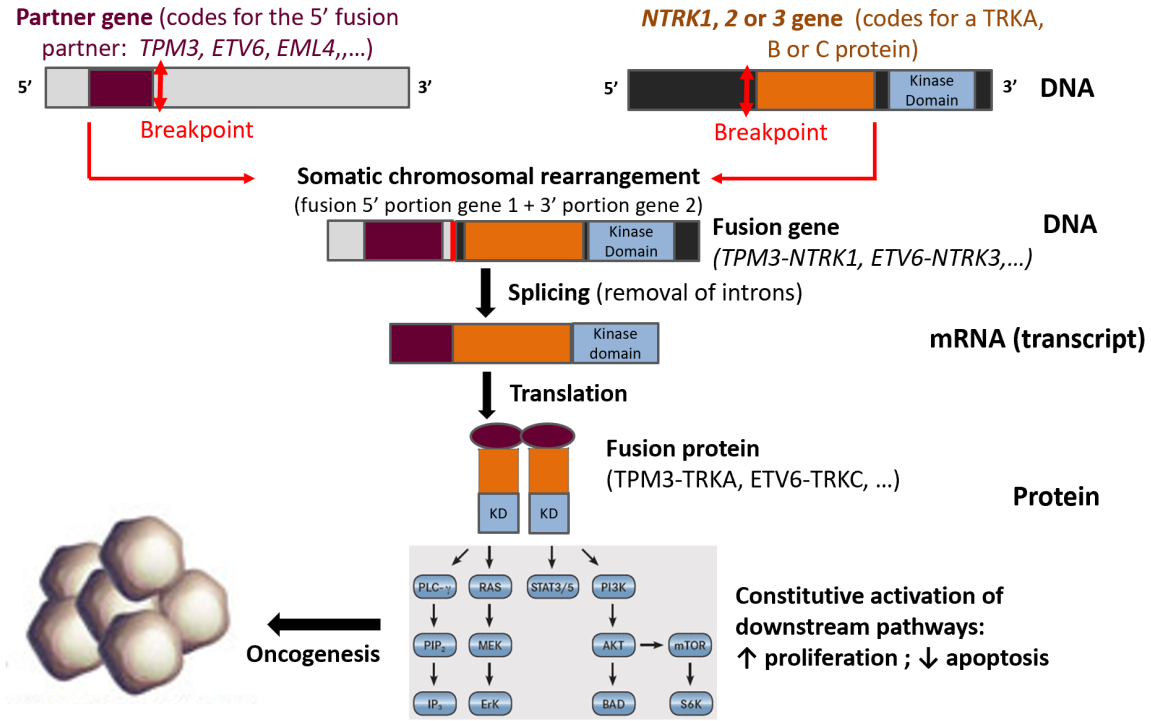
Tumour Type	TCGA		Project GENIE	
	Total samples N	NTRK n (%)	Total samples N	NTRK n (%)
All tumour types	5221	35 (0.67%)	41882	83 (0.2%)
NSCLC	517	1 (0.19%)	8559	9 (0.11%)
Melanoma	468	1 (0.21%)	2291	5 (0.21%)
CRC	557	3 (0.54%)	5795	7 (0.12%)
Pancreas	178	2 (1.12%)	1966	5 (0.25%)
Breast Cancer	1026	2 (0.19%)	8075	9 (0.11%)

2.1.3. Biologic features

Tropomyosin receptor kinase receptors (TRKs) are a family of tyrosine kinases that bind neurotrophins, a family of growth factors important for the formation and function of the nervous system. TRKA, TRKB and TRKC receptors are encoded by the neurotrophic receptor tyrosine kinase *NTRK*1, *NTRK*2, and *NTRK*3 genes, which are located on human chromosomes 1q23.1, 9q21.33, and 15q25.3, respectively. The overall structure of the TRK proteins is conserved, and the three TRK proteins show 40% amino acid identity overall. In normal signalling process, the binding of neurotrophins to TRK receptors leads to the activation of various downstream signalling pathways, such as those involving RAS, PI3K and PLC 1–4[1234].

In cancer, the *NTRK*1, *NTRK2*, and *NTRK*3 genes are subject to gene rearrangements that lead to kinase domain expression and constitutive downstream pathway activation. In these somatic rearrangements, the 5' portion of a gene which is expressed by the tumour cell progenitor is fused to the 3' portion of one of the three *NTRK* genes. This fusion gene is then transcribed into an mRNA fusion transcript which codes for a fusion protein containing the N-terminus of the fusion partner (usually containing a dimerization domain) and the C-terminus of one of the TRK proteins, including the kinase domain (Figure 1).

[1] Khotskaya, Y. B. *et al* Targeting TRK family proteins in cancer. *Pharmacol Ther* **173**, 58–66 (2017).
[2] Brodeur, G. M. et al. Trk receptor expression and inhibition in neuroblastomas. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 15, 3244–3250 (2009).
[3] Reichardt, L. F. Neurotrophin-regulated signalling pathways. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 361, 1545–1564 (2006).
[4] Valent, A., Danglot, G. & Bernheim, A. Mapping of the tyrosine kinase receptors trkA (NTRK1), trkB (NTRK2) and trkC(NTRK3) to human chromosomes 1q22, 9q22 and 15q25 by fluorescence in situ hybridization. Eur. J. Hum. Genet. EJHG 5, 102–104 (1997).



Schematic representation of a fusion between an *NTRK* gene and a partner gene, and the resulting production of an *NTRK* fusion gene, an *NTRK* fusion transcript and a TRK fusion protein. During these gene rearrangements, the 3' portion of the *NTRK* gene which encodes the tyrosine kinase domain of a TRK protein is fused to the 5' part of a fusion partner.

Figure 1: Schematic representation of a NTRK gene fusion

NTRK gene fusions could occur in 0.3 to 1% of all solid tumours [5][6][7] , and involve mainly the *NTRK*1 and *NTRK*3 genes, and multiple 5' fusion partners (over 60 different partner genes to date)[8]. These rearrangements are present at a low frequency in common tumour types, but at very high frequency in rare paediatric and adult tumours, such as infantile fibrosarcoma (with mainly ETV6-*NTRK*3 fusions, but other *NTRK*3 fusions as well *NTRK*1 fusions have also been identified), congenital mesoblastic nephroma (mainly *NTRK*3 fusions described to date), mammary analogue secretory carcinoma of the salivary gland and secretory carcinoma of the breast (in both tumour types, ETV6-*NTRK*3 is the most frequent fusion).

2.1.4. Clinical presentation, diagnosis

The sought indication concerns a disease setting of locally advanced or metastatic malignant solid tumours after standard therapy or when there is no appropriate available therapy. In this setting symptoms of disease will be present or imminent and the disease is incurable, likely leading to death.

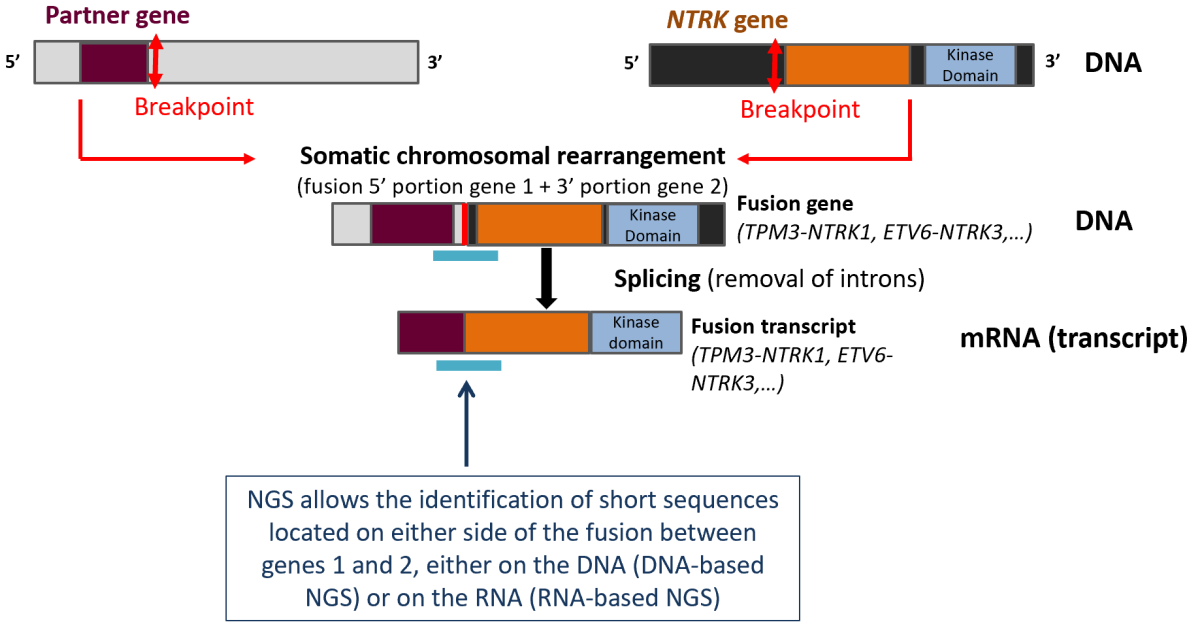
Several molecular tools are currently available for the detection of NTRK fusions in tumour specimens:

- **Fluorescence in situ hybridization (FISH)** allows the detection of *NTRK*1, 2, or 3 gene rearrangements on the DNA using break-apart probes specific for the *NTRK*1, 2, or 3 genes (a different FISH analysis must be performed for each of the 3 *NTRK* genes) (Figure 2). This technique allows the detection of an *NTRK* rearrangement but does not give any indication on the nature of the

[5] Stransky, N., Cerami, E., Schalm, S., Kim, J. L. & Lengauer, C. The landscape of kinase fusions in cancer. Nat. Commun. 5, 4846 (2014).
[6] 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).
[7] Drilon, A. et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N. Engl. J. Med. 378, 731–739 (2018).
[8] Kummar, S. & Lassen, U. N. TRK Inhibition: A New Tumor-Agnostic Treatment Strategy. Target. Oncol. 13, 545–556 (2018).

fusion partner and might give some false-positive results as some NTRK gene rearrangements detected on DNA might not produce a fusion transcript[9].

- **Next generation sequencing (NGS)** assays on tissue DNA (for example MSK-IMPACT, FoundationOne) or RNA (Archer FusionPlex, OmniSeq comprehensive, Thermo Fisher Oncomine Focus), could allow the full characterization of the genes involved in the fusion (rearranged gene and partner gene). However, the DNA panels currently used may not be designed to detect all possible *NTRK* fusions. Indeed, the FoundationOne panel, does not include *NTRK*3 fusions, and has only partial intron coverage for *NTRK*1 and *NTRK*2 10. Concerning the MSK-IMPACT assay, a recent publication reports a partial coverage for *NTRK*1 and *NTRK*2 and that probes for ETV6 are used for the detection of ETV6-*NTRK*3 rearrangements. Similarly, the MSK-IMPACT NGS test does not allow the detection of *NTRK*3 rearrangements but uses probes to detect ETV6 rearrangements and also has partial coverage for *NTRK*1 and *NTRK*2. Capture-based NGS methods thus have some drawbacks for the detection of *NTRK* rearrangements, which contain large introns. And, the same as with the detection with FISH, might also give rise to false-positive results as some *NTRK* gene rearrangements detected on DNA appear not to produce a fusion transcript 11. The use of an RNA-based NGS method for the detection of *NTRK* gene rearrangements could seems more adequate. Indeed, these techniques allow the detection of *NTRK* fusions without the need to cover the intronic regions (which are spliced out), and detect fusions which will result in an expressed fusion protein (Figure 2: Schematic representation of the detection by NGS of a NTRK fusion).



Schematic representation of the detection by NGS of a fusion between an NTRK gene and a partner gene by NGS, either on the DNA (detection of the fusion gene by DNA-based NGS) or from the RNA (detection of the fusion transcript by RNA-based NGS).

Figure 2: Schematic representation of the detection by NGS of a NTRK fusion

- **Reverse-transcription PCR (RT-PCR)** also allows the detection of *NTRK* fusion transcripts, but requires the use of a high number of primer pairs to be able to detect all potential fusions possible (high risk of false-negatives considering the diversity of *NTRK* fusions possible). A possible adaptation of this technique could be to use primers to detect amplicons located the 5' and 3'

[9] Hechtman, J. F. et al. Pan-Trk Immunohistochemistry Is an Efficient and Reliable Screen for the Detection of NTRK Fusions. Am. J. Surg. Pathol. 41, 1547–1551 (2017).

portions of each of the *NTRK* gene and look for an imbalance of the ratio between the 5' and 3' amplicons produced.

- **Immunohistochemistry (IHC)** can also be used to detect TRK fusion proteins. A pan-TRK antibody (clone EPR17341) has been used to detect a homologous region of TRK -A, TRK -B and TRK -C. This antibody was compared to molecular analyses by NGS and showed a sensitivity of 95.2% (detection of 95.2% of positive cases) and a specificity of 100% (no false-positives) compared to RNA-sequencing (Archer FusionPlex)[10]. Another study used the same antibody to detect TRK fusions in paediatric mesenchymal tumours, and yielded a sensitivity and specificity of 97 and 98%, respectively, by comparison with DNA-based NGS. This IHC assay could be a useful cost-effective and easily implemented screening tool for the detection of very rare cases of TRK-positive tumours, and the *NTRK* rearrangement could then be confirmed by RNA-sequencing. However, this tool must be validated against a sufficient cohort of NTRK-positive and –negative cases.

2.1.5. Management

The sought indication encompasses all malignant solid tumours types that have an NTRK gene fusion, with the exception of primary CNS tumours, and concerns a disease setting after standard therapy or when there is no appropriate available therapy. The intention of therapy in this setting is palliative.

There are currently no approved specific targeted therapies for patients with TRK fusion cancer, nor are there any national consensus guidelines or literature references with recommendations for the clinical management of patients with TRK fusion cancer. Patients with advanced TRK fusion cancer are clinically managed based on care standards for the tumour site of origin.

Initial treatments at primary diagnosis include surgery and radiotherapy; and for thyroid cancers, radioactive iodine. Systemic therapy options (including chemotherapy and treatment with biologics) are subsequently considered.

The therapeutic modalities for different types of locally advanced and metastatic malignant solid tumours (the present disease setting) may include:

- Surgery (palliative)
- Systemic therapy: cytotoxic/cytostatic chemotherapy, targeted therapy, immunotherapy, hormonal therapy
- Radiation therapy

It should be noted that for several rare tumour types, such as salivary gland cancer and IFS, randomized trials establishing best practices have not been conducted. For other tumour types, such as soft tissue sarcoma, care standards are generally associated with low response rates of modest duration.

Different systemic treatment options by tumour type are summarized in Table 3: Summary of Current Systemic Treatment Options for Advanced/Metastatic Disease in Selected Tumour Types (includes patients with and without NTRK fusion) (Table 3) although these therapies may not be approved for use in all countries. None of these treatments have been developed for, or specifically studied in subgroups of patients with NTRK gene fusions so available data reflect the efficacy in the general disease population.

Overall, for patients with advanced NTRK fusion-positive cancer, there are only few treatment options available if standard treatment has failed. For some patients no treatment options are available. For many patients, ongoing salvage treatment with existing alternatives is not considered beneficial due to known

[10] Rudzinski, E. R. et al. Pan-Trk Immunohistochemistry Identifies NTRK Rearrangements in Pediatric Mesenchymal Tumors. Am. J. Surg. Pathol. 42, 927–935 (2018).

toxicities of available treatments or co-morbidities of the patient which predict for deterioration in quality of life with ongoing therapy.

Table 3: Summary of Current Systemic Treatment Options for Advanced/Metastatic Disease in Selected Tumour Types (includes patients with and without NTRK fusion)

Tumour Type	First-line	Second-line	Further lines
Soft tissue sarcoma	Doxorubicin +/- olaratumab or ifosfamide or docetaxel, paclitaxel, gemcitabine	Trabectedin, pazopanib, eribulin, pacllitaxel	None
Salivary gland carcinoma	Platinum/doxorubicin, paclitaxel, vinorelbine, mitoxantrone, cetuximab+cisplatin, gefitinib+lapatinib, clinical trials	None	None
Infantile fibrosarcoma	Vincristine, actinomycin, and cyclophosphamide (VAC),vincristine, doxorubicin, and cyclophosphamide (CAV),ifosfamide, vincristine, and actinomycin (IVA), vincristine, actinomycin, ifosfamide, and doxorubicin (VAIA). Vincristine and actinomycin (VA)	None	None
Colorectal cancer	FOLFOX, FOLFIRI, CAPOX, FOLFOXFIRI, or fluoropyrimidine bevacizumab, cetuximab, pantimumuab	FOLFOX, XELOX, FOLFIRI, cetuximab, panitumumab, aflibercept, ramucirumab	Cetuximab, panitumumab, irinotecan, regorafenib, trifluridine/ tipiracil
Thyroid cancer (non-medullary)	Doxorubicin, sorafenib, lenvatinib	None	None
Anaplastic thyroid cancer	Doxorubicin +/- cisplatin, paclitaxel	None	None
Gastrointestinal stromal tumour	Imatinib	sunitinib	regorafenib
Lung cancer (EGFR and ALK negative)	Platinum doublet, pemextrexed	Pemextrexed, docetaxel, nivolumab, nintedanib / docetaxel, ramucirumab / docetaxel / pembrolizumab, afatinib	None
Lung cancer (EGFR and ALK mutated)	Erlotinib, gefitinib, afatinib, crizotinib	Osimertinib, alectinib	None
Malignant melanoma	Pembrolizumab, nivolumab, vemurafenib, dabrafenib, dacarbazine temozolomide	pembrolizumab, nivolumab, vemurafenib, dabrafenib	None

Abbreviations: ALK = anaplastic lymphoma kinase; CAPOX or XELOX = capecitabine + oxaliplatin; EGFR = epidermal growth factor receptor; FOLFOX = folinic acid + fluorouracil + oxaliplatin; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOXFIRI = folinic acid + fluorouracil + oxaliplatin + irinotecan

A comparison of larotrectinib with available systemic treatments by tumour type is presented in **Table 76**.

About the product

Mode of action, Pharmacological classification

Larotrectinib is an adenosine triphosphate (ATP) competitive and selective tropomyosin receptor kinase (TRK) inhibitor that was rationally designed to avoid activity with off target kinases. The target for larotrectinib is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by NTRK1, NTRK2 and NTRK3 genes, respectively. In a broad panel of purified enzyme assays, larotrectinib inhibited TRKA, TRKB, and TRKC with IC50 values between 5 and 11 nM. The only other kinase activity occurred at 100 fold higher concentrations. In in vitro and in vivo tumour models, larotrectinib demonstrated anti-tumour activity in cells with constitutive activation of TRK proteins resulting from gene fusions, deletion of a protein regulatory domain, or in cells with TRK protein overexpression.

In frame gene fusion events resulting from chromosomal rearrangements of the human genes NTRK1, NTRK2, and NTRK3 lead to the formation of oncogenic TRK fusion proteins. These resultant novel chimeric oncogenic proteins are aberrantly expressed, driving constitutive kinase activity subsequently activating downstream cell signalling pathways involved in cell proliferation and survival leading to TRK fusion positive cancer.

Pharmaceutical presentations

- Hard capsules 25 mg and 100 mg
- Oral solution 20 mg/ml

The applicant applied for the following indication:

"Vitrakvi is indicated for the treatment of adult and paediatric patients with locally advanced or metastatic solid tumours (excluding primary central nervous system (CNS) tumours) with a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion after prior standard therapy or as initial therapy when there is no adequate treatment option."

The recommended indication is:

"VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display 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 no satisfactory treatment options (see sections 4.4 and 5.1)."

Treatment with VITRAKVI should be initiated by physicians experienced in the administration of anticancer therapies.

The presence of an NTRK gene fusion in a tumour specimen should be confirmed by a validated test prior to initiation of treatment with VITRAKVI.

VITRAKVI is for oral use and is available as a capsule or oral solution with equivalent oral bioavailability, and may be used interchangeably

The recommended dose in adults is 100 mg larotrectinib twice daily, until disease progression or until unacceptable toxicity occurs.

Dosing in paediatric patients is based on body surface area (BSA). The recommended dose in paediatric patients is 100 mg/m2 larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or until unacceptable toxicity occurs.

If a dose is missed, the patient should not take two doses at the same time to make up for a missed dose. Patients should take the next dose at the next scheduled time. If the patient vomits after taking a dose, the patient should not take an additional dose to make up for vomiting.

For all Grade 2 adverse reactions, continued dosing may be appropriate, though close monitoring to ensure no worsening of the toxicity is advised. Patients with Grade 2 ALT and/or AST increases, should be followed with serial laboratory evaluations every one to two weeks after the observation of Grade 2 toxicity until resolved to establish whether a dose interruption or reduction is required.

For Grade 3 or 4 adverse reactions:

- VITRAKVI should be withheld until the adverse reaction resolves or improves to baseline or Grade 1. Resume at the next dose modification if resolution occurs within 4 weeks.
- VITRAKVI should be permanently discontinued if an adverse reaction does not resolve within 4 weeks.

The recommended dose modifications for VITRAKVI for adverse reactions are provided in Table 1.

Table 4: Recommended dose modifications for VITRAKVI for adverse reactions

Dose modification	Adult and paediatric patients with body surface area of at least 1.0 m2	Paediatric patients with body surface area less than 1.0 m2
First	75 mg twice daily	75 mg/m2 twice daily
Second	50 mg twice daily	50 mg/m2 twice daily
Third	100 mg once daily	25 mg/m2 twice daily

VITRAKVI should be permanently discontinued in patients who are unable to tolerate VITRAKVI after three dose modifications.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on:

NTRK fusion events appear to be important oncogenic drivers in tumours bearing them, in the sense that inhibition with Larotrectinib causes significant tumour shrinkage in a large proportion of patients. It is unlikely that other approved drugs or combinations of drugs could parallel this activity in at least part of the presently aimed for target population. Pending final wording of the indication, alternatives are

expected to be exhausted in the "progressed following prior treatment or no acceptable alternative treatments" population.

The application is further considered innovative, as the complication of NTRK fusion rarity has been approached with a tissue-independent development program.

However, the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as the uncertainties raised during the assessment required a thorough review of the quality, clinical pharmacology and clinical efficacy aspects.

During the assessment, the applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data. The applicant proposed to submit the study report from ongoing studies (LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003) and a single arm, multi-cohort, prospective non-interventional study (PASS) conducted to verify and describe the clinical benefit of larotrectinib.
- Unmet medical needs will be addressed, as the proposed indication for larotrectinib places the product in a setting where no satisfactory treatment options remain since patients will have failed to respond to standard of care, did not tolerate it or do not have any standard of care for treatment.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. The applicant claims that NTRK gene fusion events are important oncogenic drivers and the activity of larotrectinib has demonstrated significant tumour shrinkage in a large proportion of patients. Based on the proposed indication, patients eligible for larotrectinib will have exhausted all satisfactory treatment options. In addition, the known risks are considered acceptable given the life-threatening nature of metastatic solid tumours with limited or no available therapy, given the observed magnitude of effect on ORR.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as:

A. Hard capsules containing 25 mg or 100 mg of larotrectinib sulfate as active substance.

Other ingredients are:

Capsule shell: gelatin, titanium dioxide (E 171)

Printing ink: shellac, indigo carmine aluminium lake (E 132), titanium dioxide (E 171), propylene glycol (E 1520), dimeticone.

The hard capsules is available in high density polyethylene (HDPE) bottles with a child resistant polypropylene (PP) cap with a polyethylene (PE) heat seal layer, as described in section 6.5 of the SmPC.

and,

B. Oral solution containing 20 mg/mL of larotrectinib sulfate as active substance.

Other ingredients are: purified water, sucrose, hydroxypropylbetadex, glycerol (E 422), sorbitol (E 420), sodium citrate (E 331), sodium dihydrogen phosphate dihydrate (E 339), citric acid (E 330), propylene

glycol (E 1520), potassium sorbate (E 202), methyl parahydroxybenzoate (E 218), citrus fruit flavour, and natural flavour.

The oral solution is available in amber glass (type III) bottle with a child resistant polypropylene (PP) cap with a polyethylene (PE) seal liner, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of larotrectinib sulfate is (3*S*)-N-{5-[(2*R*)-2-(2,5-difluorophenyl)-1-pyrrolidinyl]pyrazolo[1,5-a]pyrimidin-3-yl}-3-hydroxy-1-pyrrolidinecarboxamide sulfate corresponding to the molecular formula $C_{21}H_{24}F_2N_6O_6S$. It has a relative molecular mass of 526.51 g/mol and the following structure:

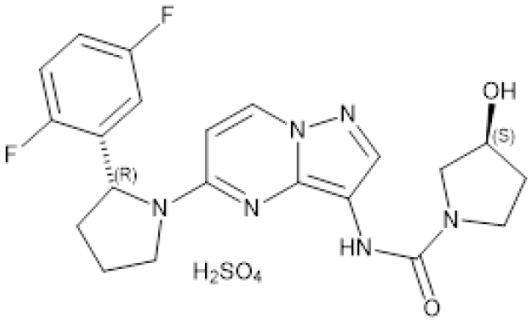


Figure 3: active substance structure

The chemical structure of larotrectinib was elucidated by a combination of mass spectrometry, ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, infrared spectroscopy, ultraviolet–visible spectrophotometry, specific optical rotation and element analysis.

The solid state properties of the active substance were measured by single crystal X-ray diffraction analysis.

The active substance is off-white to yellow to pinkish yellow, non-hygroscopic powder. The solubility of larotrectinib sulfate is low in most organic solvents with the exception of the alcohols, specifically methanol and ethanol. The aqueous solubility of larotrectinib sulfate is pH dependent. *In vitro* studies show that in liquid volumes relevant to the gastrointestinal (GI) tract larotrectinib is fully soluble over entire pH range of the GI tract. Therefore, larotrectinib sulfate can be classified as highly soluble according to the Biopharmaceutical Classification System (BCS) criteria. Although a formal assessment of biopharmaceutical class has not been performed, larotrectinib sulfate has the attributes of a BCS Class 1 compound, characterized by high solubility and high permeability.

Larotrectinib exhibits stereoisomerism due to the presence of two chiral centres. Stereoisomerism originates from the starting materials and enantiomeric purity is controlled routinely by chiral High Performance Liquid Chromatography (HPLC) in the active substance specification with limits for the enantiomer and two diastereomers.

Polymorphism has been observed for larotrectinib sulfate. Extensive polymorph screening and evaluation studies have been conducted on the active substance. The results from these screening studies showed only one crystalline form or amorphous material from. To date, only a single form of larotrectinib sulfate has been consistently produced in the manufacturing of the active substance and has been physically stable in all active substance stability programs, including those under stress conditions.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the dossier and it was considered satisfactory. The active substance is obtained from a single manufacturer.

Larotrectinib sulfate is synthesized in four main steps and the salt formation step using three well defined starting materials with acceptable specifications. Three intermediates are isolated.

The first synthetic step consists of coupling of two starting materials. It is followed by a reduction step and acylation. The synthesis continues with reaction with the third starting material and treatment with sulfuric acid to provide larotrectinib as the sulfate salt. The reactions are performed in inert atmosphere, in appropriate vessels, with agitation and at the specified temperatures. No materials used in the process are recovered or recycled.

Three starting materials were initially proposed. All three proposed starting materials have defined chemical structures and together provide the key structural features of the finished active substance. Compounds 1 and 2 are made by custom synthesis. No fundamental objections were made to the designation of 1 and 2 as starting materials and their specifications are acceptable.

However, compound 3 could not be accepted due to insufficient control of its stereochemistry and impurities. Also, the claim that Compound 3 is commercially available could not be sufficiently substantiated. These concerns constituted a Major Objection and a redefinition of Compound 3 to an intermediate and assignment of an earlier precursor as starting material was therefore requested by CHMP. As all necessary activities related to the redefinition could not reasonably be expected to be resolved within the time frame of the procedure, a Post-Approval Change Management Protocol (PACMP) was proposed. The submitted PACMP contains details and justifications on the activities and timelines for the redefinition of the starting material and it is considered acceptable.

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

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 different manufacturer has been used for production of early clinical and toxicology batches; however the same synthetic route has been applied throughout the process development. The bridging is supported by the provided batch analyses and stability studies.

The active substance is packaged in bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. The bags are closed and placed in a drum.

Specification

The active substance specification includes tests for: appearance, identity (FTIR, HPLC), assay H_2SO_4 salt (HPLC), freebase potency (HPLC), HPLC purity (HPLC), impurities (HPLC), chiral purity (chiral HPLC), sulfate content (HPLC), elemental impurities (ICP-MS), residue on ignition (Ph. Eur.), water content (KF), residual solvents (GC), particle size (laser diffraction).

A single impurity present at higher than the qualification threshold according to ICH Q3A was qualified by toxicological and clinical studies and appropriate specifications have been set.

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 on 6 commercial scale batches of the active substance are provided. Additionally, batch analysis from 4 supporting batches manufactured using earlier processes. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from four commercial scale and one approximately two thirds of commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Data on four additional supportive batches was provided.

The stability studies on the registration batches were performed using the same analytical methods up through the 3-month time point. From the 6-month time point improved versions of the methods for chiral and achiral impurities as well as water content were implemented. Batches are tested for appearance, assay, purity, chiral purity, water content, and physical form at every time point. Microbial testing is performed annually as an additional test item for informative purposes.

All tested parameters were within the specifications with no trends observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. Data shows that larotrectinib sulfate is not photosensitive.

Results on stress conditions were also provided on one batch. Forced-degradation studies were conducted under thermal, photolytic, acidic, basic and oxidation conditions. The results of the forced-degradation study show that larotrectinib sulfate is very stable under stress conditions. Only limited amounts of degradation were observed under all conditions other than oxidation where significant degradation takes place.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the retest period when stored below 30 °C in the proposed container.

2.2.3. Finished Medicinal Product

A. Hard Capsules

Description of the product and Pharmaceutical development

VITRAKVI hard capsules are formulated as immediate release gelatin capsules for oral administration. The capsules are available in 2 strengths and contain 25 mg or 100 mg of neat active substance. The 25 mg capsule is provided in a white opaque hard gelatin size "2" capsule, printed with 'Bayer' cross and the strength (25 mg) in blue ink. The 100 mg capsule is provided in a white opaque hard gelatin size "0" capsule printed with 'Bayer' cross and the strength (100 mg) in blue ink. The composition of capsules is provided in the following tables.

Based on the results of Phase I clinical trials in a specific, yet limited patient population, minimal development work was done with respect to the capsule finished product. While simple blends were considered as a formulation approach, given the clinical response, and in order to expedite drug to patients, active substance in a capsule was chosen as the preferred finished product.

As discussed earlier in the report, extensive pre-formulation studies, including a comprehensive physicochemical and biopharmaceutical characterization of the larotrectinib sulfate active substance, polymorph screening, and stability profiling were performed. It was determined that larotrectinib sulfate

is highly soluble, chemically and physically stable, and non-hygroscopic. Only a single polymorph of the active substance has been identified under active substance and finished product processing and storage conditions, and this form has been consistently produced and used during development.

The active substance manufacturing process produces the active substance of consistent particle size. Due to aqueous solubility of larotrectinib sulfate, particle size is not considered a critical quality attribute to ensure consistent dissolution rate.

The simple active substance in capsule formulation was chosen as it eliminates the potential for interaction with excipients. The stability of the product over time demonstrates that there is no potential for interaction between the active substance and the capsule shell. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. 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.

As the formulation is the active substance in a capsule, release is limited only by the disintegration of the gelatin capsule since, as noted previously, larotrectinib sulfate active substance is very soluble in aqueous media.

Throughout the development of Larotrectinib sulfate capsules, the used capsule has remained unchanged. Based on the pH solubility profile of larotrectinib sulfate, disintegration testing (of the gelatin capsule) has served as an adequate control on the performance of the finished product and has been included in the finished product specification as replacement of dissolution testing in accordance with ICH Q6A Guideline "Specifications: Tests procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances". However, a dissolution method has been developed and validated. Based on the results of dissolution development studies, a method was developed. The discriminatory power of the dissolution method has been demonstrated.

The formulation used during clinical studies is the same as that intended for marketing.

The primary packaging is HDPE bottles. 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

Manufacture of VITRAKVI capsules consists of three main steps: filling larotrectinib sulfate active substance into hard gelatin capsules by weight, placing the finished capsules into high-density polyethylene bottles and induction sealing. The capsule filling technology uses a gravimetric filling method to fill unit doses of active substance directly into capsules. The system uses a metering technology controlled via software to accurately fill capsules. Each capsule is opened, filled, closed, and weighed during the process and any that are outside of the acceptable weight range are rejected. After evaluation of all relevant manufacturing steps in order to identify the risk areas to be targeted during process validation, no steps were identified as having a high risk to quality with the proposed process.

The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. No critical steps have been identified. 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: appearance, identity (HPLC, UV), assay (HPLC), degradation products (HPLC), chiral purity (chiral HPLC), water content (KF), dose uniformity by weight variation (Ph. Eur.), dissolution after 45 minutes (Ph. Eur.), microbial enumeration testing (Ph. Eur).

Residual solvents are controlled in the active substance. No solvents are used during finished product manufacture and the capsule shells do not contain residual solvents. Therefore, the absence of a residual solvent specification for VITRAKVI capsules is justified.

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

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 13 batches of different scales (6 of those commercial) for 25 mg capsules and 12 batches of different scales (7 of those commercial) for 100 mg capsules, 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

Stability data from eight 25 mg capsule batches manufactured up to the commercial scale and from nine 100 mg capsule batches manufactured up to the commercial scale and stored for up to 12 months under long term conditions (25 ºC / 60% RH), up to 12 months under intermediate 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 medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same parameters as for release with the exception of identification and dose uniformity. The analytical procedures used are stability indicating. No significant changes have been observed and all results remained within the acceptance criteria.

In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch of each of the capsule strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products and on twice the amount as defined in the Guideline. There were no significant changes to chromatographic purity at 1x or 2x ICH light exposure. All larotrectinib sulfate peaks are considered spectrally pure. Light exposure, at 1x and 2x ICH light exposure recommended levels, does not adversely affect the larotrectinib sulfate product quality demonstrating its photostability.

Additionally, a study has been designed to confirm in-use stability of the capsules in their proposed commercial container closure systems, without desiccant. The study is performed with one batch of each of the capsule strengths. No significant changes over time are seen and the data indicates acceptable in-use stability. No shelf life after first opening of the container needs to be stated in the SmPC.

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

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

[2]6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

B. Oral Solution

Description of the product and Pharmaceutical development

VITRAKVI 20 mg/mL oral solution consists of 100 mL of clear yellow to orange oral solution formulation filled into a 100 mL amber Type III glass bottle with a child-resistant PP cap and a PE tamper-evident seal liner.

The composition of the finished product is presented in the following table.

Based on the results of larotrectinib in Phase I clinical trials in a rare, orphan patient population, a liquid formulation was developed for a pediatric population with tumors harboring NTRK gene fusions. This development effort initially focused on achieving a balance between solubility and pH – as larotrectinib sulfate is extremely soluble at low pH. However, low pH would pose palatability issues for the patient. Various solubility enhancers were considered, focusing on those that would be acceptable in a pediatric population in terms of taste, while keeping the pH at the level of most fruit juices. Once this had been accomplished using a hydroxypropyl-beta-cyclodextrin (HPβCD) and sodium citrate, the focus turned to masking the extremely bitter taste of larotrectinib sulfate. This was accomplished by utilizing commercially available excipient mixture intended as a vehicle for drug administration, as well as multiple masking agents and flavorings.

During the assessment, a Major Objection was raised concerning the lack of information about the quantitative composition of the excipient mixture used. In response to the questions, the applicant has included additional information about the excipient composition in the composition table and detailed analytical results have been added to the excipients section of the dossier. Major Objections were also raised since no study to determine the minimum effective concentration of preservatives according to Ph. Eur. was submitted, and regarding the lack of confirmation of compliance with the Ph. Eur. for some excipients. However, the quality of the product is sufficiently demonstrated to support approval taking into consideration the clinical benefits of the finished product and that the oral solution is proposed as an interim product. All excipients are well known pharmaceutical ingredients. 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.

During the pharmaceutical development it was found that the order of addition of the components was critical in order to achieve complete dissolution and it was noted that the colour of the solution changed on storage at 25°C/60% RH and 40°C/75% RH. It was decided to recommend storage at refrigerated conditions and that the oral solution was to be filled in glass containers.

Initially, production of clinical batches was performed at a development site and transfer was then made to the commercial manufacturing site. Similar manufacturing equipment was used at both sites and the change in scale was considered to be low risk.

The primary packaging is one hundred milliliters of a 20 mg/mL larotrectinib solution formulation filled into a 100 mL amber Type III glass bottle, PP neck and capped with a child resistant and tamper evident

closure with a PE liner. An extractable study was provided for the container closure system and it was found acceptable.

The oral solution was developed as a pediatric formulation, and the SmPC (section 4.2) states that the product can be administered by feeding tube. This is supported by a recovery study for administration of VITRAKVI solution 20 mg/mL for oral use via nasogastric feeding tubes to demonstrate the suitability of the proposed flushing volume with respect to dose recovery.

The choice of glass bottles with polypropylene caps and polyethylene liners as container/closure system is considered acceptably justified.

Manufacture of the product and process controls

The manufacturing process of the oral solution consists of three main steps: mixing of the components, filtration and filling into bottles. The process is considered to be a standard manufacturing process.

Process validation of three consecutive commercial-scale batches of the VITRAKVI oral solution has been carried out. The traditional process validation approach including enhanced sampling and testing at the mixing and filling stages was applied. No separate validation report has been submitted but a summary is given in the dossier and was found acceptable.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The mixing steps including the respective process parameters and the order of addition of components into the mixture are defined as critical steps. 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: appearance, identity (HPLC, UV), assay (HPLC), degradation products (HPLC), chiral purity (chiral HPLC), deliverable volume (USP), pH (Ph. Eur.), elemental impurities (ICP-MS), microbial enumeration testing (Ph. Eur.), and antimicrobial preservative effectiveness (USP).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The risk assessment includes adequate information regarding the intentionally added catalysts in the active substance and it is repeated that they are controlled at an acceptable level in the active substance specification.

However, as the risk assessment does not exclude the risk of intentionally added elements in excipients, testing of all elements listed in the ICH Q3D guideline is performed.

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 three stability batches of 1/5 of the commercial scale, three process validation batches as well as for clinical batches of larger batch size manufactured under similar conditions, 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

Stability data from three batches of finished product manufactured at 1/5 of the commercial scale stored for up to 12 months under long term conditions (2-8 ºC), for up to 12 months under accelerated conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The specifications for release and for shelf life are identical except for identity, deliverable volume and elemental impurities testing that are performed at release only. The analytical procedures used are stability indicating.

Supportive stability batches from the two clinical batches have also been studied to provide additional data to support the long-term stability of the product. Results from storage of the first batch for 24 months at long-term conditions and 25ºC/60% RH and for 6 months at 40ºC/75% RH are provided, while for the second batch 12 months data at long-term conditions and 25ºC/60% RH and for 6 months at 40ºC/75% RH are provided. There have been no changes on stability at the recommended storage conditions of 2 – 8 °C for the supportive clinical batches after 24 months and 12 months respectively. At 25 °C/60 % RH, the solution starts to darken at 3 months in both batches, but there is no change in impurity profile or pH. At 6 months, the color has gone from yellow to orange and there is a trend toward a slight increase in measured impurities (from ~0.1 % to ~0.2 %), but the pH remains unchanged. Assay results do not show a trend after 12 months at 25 °C/60 % RH, and are well within specification. At 40 °C/75 % RH, both lots show darkening of appearance at 1 month and significant changes in color and impurities at 3 months.

The results obtained for the three registration (primary stability) batches show no changes at the recommended storage conditions of 2 – 8 °C for 12 months. Also at storage at 25 °C/60 % RH, all results are clearly within the acceptance criteria with an unchanged assay and only minor increase of degradation products. For storage at 40 °C/75 % RH, the batches show discoloration of the solution after 1 month and significant decrease of assay as well as corresponding increase of impurities over time.

In-use stability testing was performed on one clinical batch and demonstrated no change in profile after 30 days at the recommended storage conditions of 2 – 8 °C. Therefore an in-use period of 30 days when stored at 2 – 8 °C is justified SmPC (section 6.3).

For performance of the in-use testing, the smaller bottle presentation of 60 mL has been chosen instead of the commercial 100 mL bottle, because this represents a worst case scenario as demonstrated by the provided investigations regarding the headspace volume.

In accordance with EU GMP guidelines[11], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Little degradation occurred under UV light. Although degradation has occurred, it is not significant enough for a requirement to protect the product from light, as solution stability was assessed for both samples and standards over 198 hours and 201 hours respectively, and determined to be stable when unprotected from light.

Based on available stability data, the proposed shelf-life of 24 months and storage conditions ("Store in a refrigerator at 2 – 8 °C", "Do not freeze" as stated in the SmPC (section 6.3 and 6.4) are acceptable. After first opening the product should be used within 30 days and it should not be frozen.

[11] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

Adventitious agents

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

2.2.4. Discussion and conclusions 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.

During the procedure, the Applicant was asked to redefine one of the starting materials, however, since all aspects of the starting material redefinition cannot be resolved within the time frame of the procedure, a Post Approval Change Management Protocol (PACMP) has been submitted, detailing the activities and timelines for the actions associated with the redefinition process. This protocol and approach was considered acceptable.

Two pharmaceutical formulations are applied for, an oral solution developed for paediatric use and hard capsules.

The pharmaceutical developments of the products and the manufacturing processes have been acceptably described.

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. Data has been presented to give reassurance on TSE safety.

2.2.5. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Larotrectinib was tested in pharmacodynamics, PK, and toxicology programs that were designed to characterize the nonclinical activity, disposition, and safety of larotrectinib to support its marketing authorisation in the sought indication.

Primary pharmacodynamic studies focused on testing the binding affinity of Larotrectinib to TRKA, TRKB, and TRKC in vitro, inhibition of functional activity of each kinase, as well as inhibition of cell growth in TRK-fusion cell lines. Additionally, anti-tumour activity of Larotrectinib was assessed in vivo. In secondary pharmacodynamics studies, larotrectinib was tested in vitro for off-target activity in panels of non-TRK kinases and various receptors, enzymes and nuclear targets and in vivo in several pain-related studies. Cardiovascular, respiratory and central nervous system (CNS) safety pharmacology endpoints were incorporated into study designs for the pivotal repeat-dose toxicity studies in rat and monkey. The pharmacokinetics and metabolism of larotrectinib have been examined through a series of in vitro and in vivo studies that included toxicokinetic studies.

Based on the single-dose pharmacokinetics of orally administered larotrectinib in the rat, rabbit, and monkey, BID (rat and rabbit) and QD (monkey) dosing regimens were used in the repeat-dose studies.

For the toxicology program on larotrectinib, 25 toxicity studies were completed. The following studies were also conducted: Dose range finding (DRF) embryo-foetal development (EFD) studies in SD rats and New Zealand (NZ) rabbits followed by GLP EFD studies in rats and rabbits; DRF studies in juvenile SD rats from postnatal day (PND) 7 to PND 28 (two studies) with a subsequent GLP repeat dose oral toxicity study in juvenile male and female SD rats from PND 7 through PND 70; in vitro Ames and mouse lymphoma assays, an in vivo mouse micronucleus assay, and an in vitro phototoxicity study in BALB/c 3T3 mouse fibroblasts.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In Vitro Pharmacodynamics

Binding affinity of larotrectinib for TRKA, TRKB, and TRKC In Vitro
The binding affinity of larotrectinib to human TRKA, TRKB and TRKC was determined with a fluorescence method.

Table 5: Binding Affinity of Larotrectinib for TRKA, TRKB, and TRKC In Vitro

Kinase Enzyme	IC_{50} (nM)	n
TRKA	11.5 ± 7.0	71
TRKB	5.3 ± 2.6	72
TRKC	6.4 ± 3.6	67

Functional inhibition of TRKA, TRKB, and TRKC and Constitutively-Active TRKA
Functional inhibition was studied in Chinese hamster ovary cells transfected with human TRKA, TRKB or TRKC.

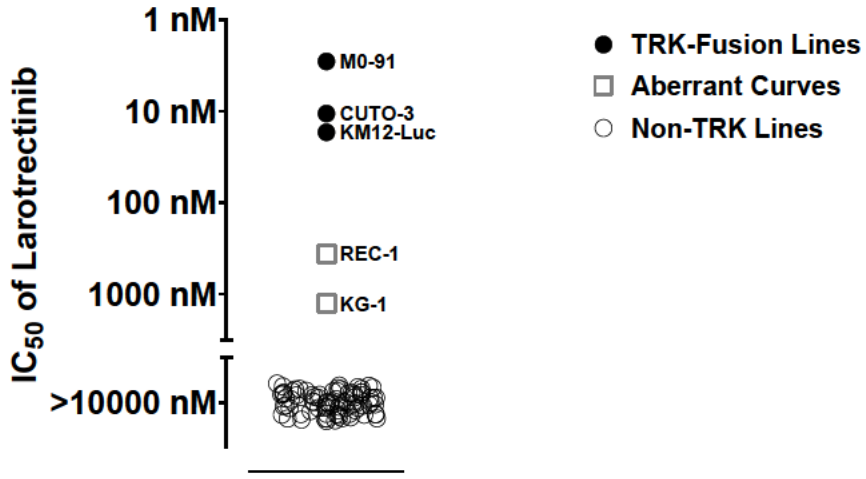
Inhibition of constitutively active TRKA was studied in NIH-3T3 cell transfected with human TRKA carrying a deletion resulting in a constitutive activity.

Table 6: Inhibition Functional Activity of TRKA, TRKB, and TRKC and Constitutively-Active TRKA

Kinase Enzyme	IC_{50} (nM)
TRKA	9.8
TRKB	25
TRKC	22
ΔTRKA (constitutively active)	6.4

Larotrectinib reduces TRKA phosphorylation in clinically-relevant NTRK1 gene fusion proteins and in cell lines derived from patients with potency in the range of 2 to 8 nM. Larotrectinib inhibits the enzymatic activity of TRKB and TRKC with potencies approximately equal to those for TRKA.

Potency of Larotrectinib on Inhibition of Cell Proliferation in Cell Lines with and without TRK-Fusion Drivers of Proliferation
Larotrectinib was incubated with 87 cancer cell lines and its IC_{50} for inhibition of proliferation was determined (LOXO-101-PHARM-033). Larotrectinib only showed potent inhibition in cell lines in which proliferation is driven by a TRK fusions. Its IC_{50} in cell lines without TRK fusion drivers was >10,000 nM.



REC-1 and KG-1 IC_{50} values were considered artefactual due to lack of any concentration-response (inhibition of 39% and 44% at 10000 nM, respectively)

Figure 4: Potency of Larotrectinib on Inhibition of Cell Proliferation in Cell Lines with and without TRK-Fusion Drivers of Proliferation

In Vivo Pharmacodynamics

Reduction of TRKA Phosphorylation in Tumors of Nude Mice Given an Oral Dose of Larotrectinib or Vehicle

Deletion of the second immunoglobulin domain (Ig2) of human NTRK1 leads to a TRKA receptor (termed ΔTRKA) that is constitutively active. NIH-3T3 cells were stably transfected with human NTRK1 with a deletion resulting in constitutive activity (ΔTRKA). The cells were implanted subcutaneously into the flanks of nude mice. Plasma and tumor samples were collected at 1, 4 and 12 hours after larotrectinib administration. Larotrectinib caused a dose- and time-dependent inhibition of TRKA phosphorylation.

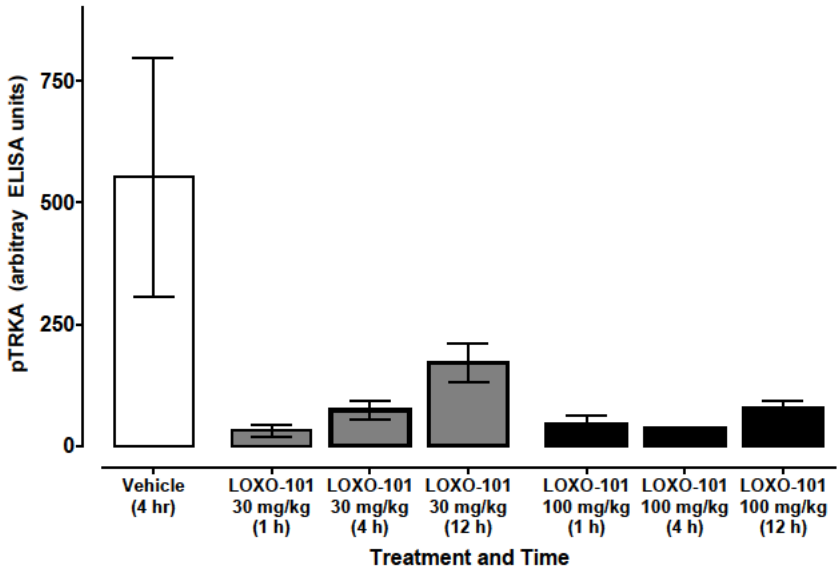


Figure 5: Reduction of TRKA Phosphorylation in Tumors of Nude Mice Given an Oral Dose of Larotrectinib or Vehicle

Inhibition of TRKA-Mediated Tumour Growth in Mice

NIH-3T3 cells stably transfected with ΔTRKA were implanted subcutaneously into the flanks of nude mice

(Ncr:Nu/Nu) and the xenograft tumours were allowed to grow to a volume of approximately 100 mm^3. Mice were dosed orally with larotrectinib or vehicle BID or daily for 14 days. Larotrectinib caused a dose-dependent inhibition of tumour growth relative to vehicle. Group mean body weight did not exceed 5% and there were no drug-related deaths.

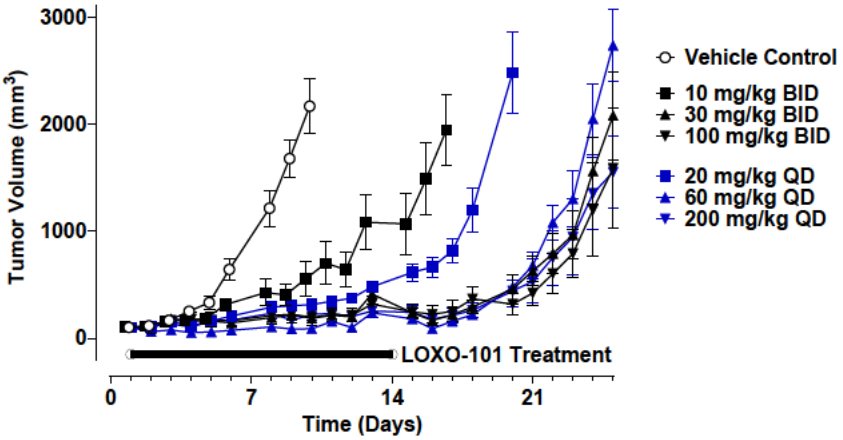


Figure 6: Inhibition of Tumour Growth in Nude Mice Implanted with NIH-3T3 cells Stably Transfected with ΔTRKA and Given Oral Doses of Larotrectinib or Vehicle

Inhibition of TRKA-mediated tumour growth in KM12 cell line

The patient-derived cell line KM12, expressing a TRK fusion was implanted subcutaneously into the flanks of nude mice. Larotrectinib at 100 mg/kg BID or 200 mg/kg QD for 7 days caused inhibition of tumor growth. Group mean body weight did not exceed 5% and there were no drug-related deaths.

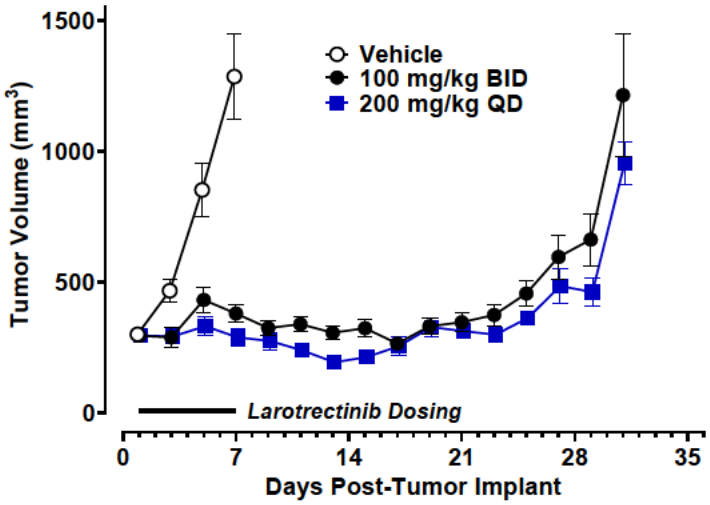


Figure 7: Inhibition of Tumour Growth in Nude Mice Implanted with KM12 Cells and Given Oral Doses of Larotrectinib or Vehicle

Secondary pharmacodynamic studies

Larotrectinib at 1 µM showed no significant inhibition of any of the non-TRK kinases tested (n=229) with the exception of TNK2, which was inhibited with an IC_{50} of 1.2 µM which is approximately 100-fold weaker than its potency against TRKA, TRKB, and TRKC (LOXO-101-PHARM-001).

Larotrectinib at a concentration of 10 µmol/L had no significant interaction with 58 potential mammalian off-targets (including G protein-coupled and nuclear receptors, ion channels, and transporters) in radioligand binding assays (LOXO-101-PHARM-019).

In another set of receptor binding, functional cellular, and enzyme assays, larotrectinib at concentrations of 10-30 µM did not displace specific ligands of mostly human receptors (D_{2S}, D_{2L}, D_3, H_3, MT_2, M_1, M_2, M_3, NK_1, σ_1, σ_2), and the human dopamine transporter. At a concentration of 30 µM, larotrectinib had no agonistic or antagonistic effect at A_1 or MT_1 receptors in cellular functional assays, and at a concentration of 10 µM, it did not inhibit the activity of human PDE4 A_{1A} (LOXO-101-PHARM-020).

Larotrectinib, at concentrations up to 100 µM (the highest concentrations tested), had no agonistic or antagonistic effect at the human nuclear receptors PPARα, PPARβ, PPARγ, RXRα, RXRβ, RXRγ, PXR, and CAR or murine PPARα, rat PPARα, or murine/rat PPARγ (LOXO-101-PHARM-021).

Safety pharmacology programme

The safety pharmacology of larotrectinib was evaluated in stand-alone in vitro and in vivo studies that assessed effects on the CNS, CV (including ECG), respiratory, and GI systems in various species (mouse, rat, dog, cynomolgus monkey). In addition, cardiovascular, respiratory and central nervous system (CNS) safety pharmacology endpoints were incorporated into study designs for the GLP repeat-dose toxicity studies in adult and juvenile rat and monkey.

Larotrectinib had no major adverse effects on CNS function up to 100 mg/kg in adult rats following both single and repeated (4 and 13 weeks) dosing (single dose: up to ~8-fold higher C_{max} than at human therapeutic dose). Larotrectinib had no neurobehavioural findings in adult animals (rats, mice, cynomolgus monkeys) at exposure (Cmax) at least 7 fold higher than the human exposure. In juvenile rats, findings indicating CNS involvement were observed, as presented below in the Toxicology section.

No adverse CV effects were noted in a conscious rat non-GLP study (up to 300 mg/kg) and a monkey GLP study in which telemetry-instrumented animals were dosed up to 100 mg/kg (~6-fold higher C_{max} than at human therapeutic dose). Larotrectinib inhibited the hERG K^+ current at an IC_{50} value of 147 µM which is approximately 230-fold higher than the maximum unbound concentration ($C_{max.u}$ = 0.68 µM) at the human dose regimen of 100 mg BID.

Larotrectinib had no effect on respiratory function in rats; at exposures (Cmax) at least 8 times the human therapeutic exposure. In rats, larotrectinib accelerated intestinal transit and increased gastric secretion and acidity (see section 5.3 of the SmPC).

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been submitted.

2.3.3. Pharmacokinetics

Larotrectinib concentrations in plasma were determined with validated LC-MS methods in GLP toxicity studies in rat, rabbit and monkey.

Absorption

Pharmacokinetic studies demonstrated oral bioavailability of approximately 30% to 150% in mice, rats, dogs, and monkeys. The pharmacokinetics following multiple doses of larotrectinib in mice, rats, rabbits,

and monkeys were generally consistent with single-dose pharmacokinetics. In general, except for rats, no significant pharmacokinetics (PK) differences with regard to sex were observed in animal species.

Distribution

The volume of distribution of larotrectinib is approximately 0.7-2 L/kg in the mouse, rat, dog, and monkey, suggesting that larotrectinib distributes into tissues. In mice, the brain/plasma ratio of larotrectinib was approximately 0.03 to 0.23 and was 3-4 fold higher in *Mdr1a*-deficient mice, which lack one of the human orthologs of *MDR1* (P-gp), and in *Mdr1a*/*Mdr1b*/*Bcrp*-knockout mice, which lack both murine orthologs of human *MDR1* and the murine ortholog of human breast cancer resistance protein (*BCRP)*. These data demonstrate low penetration of larotrectinib into the central nervous system (CNS) of mice and that transporters such as Mdr1a, Mdr1b, and Bcrp contribute to the low CNS penetration of larotrectinib in mice. The brain/plasma ratio of larotrectinib in male rats was approximately 0.01 to 0.02. Overall, these data suggest limited penetration of larotrectinib into the CNS in mice and rats.

Tissue distribution of radioactivity was evaluated by quantitative whole-body autoradiography (QWBA) in male Long Evans pigmented rats given an oral dose of [14C]-larotrectinib. Abdominal adipose, bone, eye lens, and the non-circumventricular central nervous system tissues were devoid of radioactivity throughout the time course of this study. Tissue concentrations generally declined over time. By the last sampling time of 672 hours after dosing, tissues radioactivity concentrations declined to undetectable levels (< 45 ng equivalents/g) for most tissues except for the liver and thyroid.

Plasma protein binding of larotrectinib was 56%, 64%, 55%, 61%, 66%, and 68% in plasma from mice, rats, rabbits, dogs, monkeys, and humans, respectively.

Metabolism

The one major human plasma metabolite, termed M14 (an O-glucuronide formed following loss of the hydroxypyrrolidine-urea moiety) is present in the plasma of rats and monkeys, the species used for the nonclinical safety testing of larotrectinib. The AUC of M14 in male rats (150 mg/kg BID), female rats (150 mg/kg BID), and monkeys (200 mg/kg QD) was 2-fold, 1-fold, and 20-fold higher, respectively, than the human AUC for this metabolite in cancer patients treated with 100 mg BID larotrectinib.

Excretion

Larotrectinib and its metabolites are eliminated by the renal and biliary routes. Rats eliminated 6% of an IV dose of larotrectinib in the bile as unchanged parent. Dogs excreted 71% of an intravenous dose into the urine as unchanged parent drug. Monkeys given an oral dose of radiolabeled larotrectinib excreted 27% of total drug-related material into the urine, mostly as unchanged parent drug, and 47% of the dose in the bile, mostly as metabolites.

Pharmacokinetic drug interactions

In vitro, larotrectinib is metabolized primarily by CYP3A4 with little or no metabolism by other CYP450 enzymes. Larotrectinib showed no significant direct inhibition, time-dependent inhibition, nor metabolism-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 (half maximal inhibitory concentration [IC50] of 180 µM for CYP2C8 and IC50 >300 µM for CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP2D6). However, larotrectinib showed time-dependent inhibition of CYP3A4 in vitro. Additionally, in vitro, larotrectinib showed weak induction of CYP2B6 and CYP3A4.

Larotrectinib is not a substrate of organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, OATP1B1 and OATP1B3, but is a substrate of P-gp and BCRP.

2.3.4. Toxicology

The toxicological program was conducted in line with ICH S9 recommendations and did therefore not include carcinogenicity studies and only a reduced DART program. As there is a proposed paediatric indication, a juvenile toxicity study has been conducted.

Single dose toxicity

A single dose toxicity study (LOXO-101-TOX-001, GLP) was performed in rats.

Table 7: Single-dose Toxicity Study in Rats with Larotrectinib

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings
Rat/ Sprague-Dawley	Oral Gavage Labrafac Lipophile WL 1349 (3 mL/kg)	0, 100, 300, 600	M/10 F/10	**Clinical signs:** Hypersalivation at 300 and 600 mg/kg on Day 1 ***Day 2 Results*** **Hematology:** Increase in monocytes in M at ≥ 300 mg/kg and in F at 300 mg/kg; decrease in platelets at ≥ 300 mg/kg. **Coagulation:** Prolonged prothrombin time (PT) and shortened activated partial thromboplastin time (APTT) in M at ≥ 300 mg/kg and all LOXO-101 dose groups in F. **Serum Chemistry:** Increased BUN and creatinine in M at 600 mg/kg; increase in cholesterol at 600 mg/kg; Increase in glucose in M at ≥ 100 mg/kg/day; increased alanine transaminase (ALT (both sexes)) and Total-bilirubin (M) at 600 mg/kg. **Organ Weight:** Increased heart weights in F in all LOXO-101 dose groups on Day 14.

Repeat dose toxicity

Repeat-dose toxicity was studied in rat and monkey up to 3 months. Toxicokinetic (TK) investigations were performed in all toxicity studies to determine the extent and duration of exposure of larotrectinib.

28-Day Oral Gavage Toxicity Study in the Sprague-Dawley Rat followed by a 28-Day Recovery Period

Table 8: Study Design of 28-day Repeat-Dose Study with Larotrectinib

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg)	NOAEL/STD_{10}
LOXO-101-TOX-003 GLP 28 days + 28 days recovery	Rat (SD) 10+5M /10+5F +10M/10F TK	0,10, 30, 100 BID	NOAEL: 10mg/kg STD_{10}: 100 mg/kg

Mortality: 3F at 100 mg/kg (1 main group, 2 TK) euthanized in moribund condition or found dead due to gavage error.

Clinical signs: dose-related hypersalivation, dose-related increase in skin lesions (scabs, sores, hair loss, red and swollen nose), difficulty in breathing at 100 mg/kg (1M/1F)

Body weight. Dose-related increase in body weight gain and food consumption

Hematology: decreases in red cell mass parameters and increase in reticulocytes, decreased lymphocyte counts (M), increase in monocytes at 100 mg/kg (M) and at ≥10 mg/kg (F). all haematological findings were reversible

Clinical chemistry: prolonged PT and shortened APTT (M ≥30 mg/kg, F all doses), increased fibrinogen.

Coagulation findings were considered minor, non-adverse and reversible after recovery. Dose-related increases in blood urea nitrogen and creatinine, increased cholesterol, decreased albumin (F all doses, M ≥30 mg/kg), increased blobulin (F ≥30 mg/kg, M 100 mg/kg). All changes reversible, except cholesterol in M at 100 mg/kg.

Urinalysis: increased urine volume at 100 mg/kg

Pathology, macroscopic: Mottling of the liver, scores/crusts in the skin

Organ weights: increased liver, thyroid, heart and spleen weight, decreased uterus weight. Organ weights within control values at end of recovery.

Histopathology: Minimal to moderate brown fat vacuolation (M all doses, F ≥30 mg/kg), minimal or mild hypertrophy of centrilobular hepatocytes (M 100 mg/kg F ≥30 mg/kg), increased incidence of periportal fat vacuolation, increased incidence and severity of single cell necrosis at ≥30 mg/kg, minimal to mild diffuse acinar cell hypertrophy in salivary glands at ≥30 mg/kg, increased incidence of focal dermatitis and epidermal hyperplasia in skin, epidermal crusts and ulcerations in skin, extramedullary hematopoiesis of the spleen (M all doses, F ≥30 mg/kg), minimal to moderately diffuse decrease in zymogen granules in acinar cells in pancreas (M all doses, F 100 mg/kg), focal inflammation of exocrine pancreas (M 100 mg/kg), uterine atrophy (100 mg/kg), fewer corpora lutea and greater incidence of anestrus (≥30 mg/kg), diffuse hypertrophy of the thyroid follicular epithelia (F 100 mg/kg), minimal diffuse lobular hyperplasia of mammary glands (F 100 mg/kg).

Recovery: At the end of the 28-day recovery period, microscopic changes had fully reversed in the following tissues: brown fat, female reproductive tract, liver, salivary glands, skin and spleen. Partial recovery i.e. low incidence and severity after the 28-day recovery period was observed in the following tissues: liver (females), pancreas (both sexes), salivary gland (males), spleen (males), mammary gland, and thyroid (females).

Table 9: Summary of Larotrectinib Cmax and AUC0-24 in Rat Plasma: Day 1 and 28 Mean Toxicokinetics

Dose (mg/kg/dose BID) [1]	Study Day	C_{max} (ng /mL)		AUC_{0-24} (ng*h/mL)	
		Male	Female	Male	Female
10	0	577	1200	4000	12420
	27	653	852	5600	11300
30	0	1720	3400	14140	36000
	27	4590	6100	23800	43200
100	0	5820	11200	59000	114200
	27	11300	19100	118200	198400

[1] AUC_{0-24} value was obtained by multiplying AUC_{tau} (AUC_{0-12}) by 2.

91-Day Oral (gavage) Toxicity in the Sprague-Dawley Rat Followed by a 28-Day Recovery Period

Table 10: Study Design of 91-day oral (gavage) toxicity in the Sprague-Dawley Rat

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg)	NOAEL/ STD_{10}
LOXO-101-TOX-018 GLP 91 days + 28 days recovery	Rat (SD) 10+5M /10+5F +9M/10F TK	0, 7.5, 25, 75 BID for dose reductions see below	NOAEL: 7.5 mg/kg (M), 5 mg/kg (F) STD_{10}: 17.5 mg/kg (M), 10 mg/kg (F)

Due to the progression of serious skin lesions in the mid and high dose groups, doses were lowered. Specifically, the dose level for high-dose males and females was lowered to 50 mg/kg/dose BID (twice daily) on Days 29 and 27, respectively, after females completed a dosing holiday from Day 23 (PM) through Day 26. Then on Day 42, the mid and high-dose levels for females were lowered to 10 and 20 mg/kg/dose BID, respectively. In the low dose females, scabs were noted but were not regarded as adverse at that time; however, to maintain adequate multiples of dose exposures and optimal exposures for a dose response, on Day 42 the dose was lowered in this group as well. On Day 53, dose levels for mid- and high-dose males were lowered (a second time for the high dose group) to 17.5 and 37.5 mg/kg/dose BID, respectively. Due to the serious nature of the lesions, several mid- and high-dose animals were

examined and treated with anti-inflammatory analgesics and/or antibiotics by a veterinarian on a case by case basis.

Mortality: Nine test article-related deaths in mid- and high-dose groups. Euthanasia of six out of seven moribund animals consequence of skin lesions, the seventh was sacrificed after veterinary findings including pale eyes, cold to touch and blood clots around the teeth. Two high-dose males found death, one previously under veterinary treatment for skin lesions.
Clinical signs: skin lesions, sometimes progressing to open sores
Body weight: increased body weight and food consumption (M all doses, F mid and high dose), food consumption was restricted due to hyperphagia noted in previously conducted rat studies resulting in that the body weight increase was non-adverse.
Hematology: lower red blood cell parameters, increase in neutrophil, lymphocyte and/or monocyte count, correlating with presence of inflammatory lesions in the skin
Clinical chemistry: higher serum glucose in mid and high dose groups, lower albumin and higher globulin in mid and high dose groups
Urinalysis: urine protein and blood in high dose females
Organ weights: increased thymus weight (M high dose), increased spleen weight (mid and high dose), increased liver weight (mid and high dose). A decrease in body weight adjusted prostate weight could be detected from the mid dose.
Pathology, macroscopic: skin lesions in all groups, incomplete recovery in males
Histopathology: skin lesions, with changes secondary to the skin lesions: extramedullary hematopoiesis in spleen and/or liver, lymphocyte hyperplasia of lymph nodes, and bone marrow hypercellularity. Periportal microvesicular hepatocytes, brown adipose tissue macrovesiculation, islet fibrosis, pigment and hemorrhage in the pancreas, and mammary gland hyperplasia.
Recovery: Full recovery for clinical pathology changes, organ weights. Incomplete recovery of skin lesions in males, mammary gland hyperplasia

28-Day Oral (gavage) Toxicity in the Cynomolgus Monkey Followed by a 28-Day Recovery Period

Table 11: Study Design of 28-Day Oral (gavage) Toxicity in the Cynomolgus Monkey

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg/day)	NOAEL/ HNSTD
LOXO-101-TOX-006 GLP 28 days + 28 days recovery	Cynomolgus 3+2M /3+2F	0, 10, 30, 100	NOAEL: 10 mg/kg HNSTD: 100 mg/kg

Mortality: None
Clinical signs: on day 2, a decrease in systolic and diastolic arterial blood pressures was noted at 2 hours post-dose in males at all doses
Hematology: slight decrease in red cell mass (≥30 mg/kg), prolonged PT (M ≥10 mg/kg)
Clinical chemistry: decreased albumin (≥30 mg/kg), slight increase in blood urea nitrogen, increase in AST and ALT (M 100 mg/day, 2 animals)). There were no treatment-related effects on cardiotoxicity biomarkers (pro-ANP, norepinephrine)
Organ weights: increased liver weight (all groups)
Histopathology: Liver: minimal to slight hepatocellular hypertrophy (all groups), minimal to slight parenchymal haemorrhage (≥30 mg/kg), minimal to moderate periportal lymphoid cell infiltration and slight to moderate bile duct hyperplasia (all doses), minimal single cell necrosis (≥30 mg/kg). Slight to moderate increase in the number of secondary lymphoid follicles in the mesenteric lymph node and spleen (F ≥30 mg/kg)
Recovery: all findings fully reversible

Table 12: Summary of the Mean Larotrectinib Cmax and AUC0-24 in Monkey Plasma Day 0 and 27

Dose (mg/kg/day)	Study Day	C_{max} (ng /mL)	AUC_{0-24} (ng*h/mL)
10	0	817	2990
	27	182	1290
30	0	8100	25600
	27	994	6050
100	0	27900	116000
	27	6560	32200

91-Day Oral (gavage) Toxicity in the Cynomolgus Monkey Followed by a 28-Day Recovery Period

Table 13: Study design of 91-Day Oral (gavage) Toxicity in the Cynomolgus Monkey

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg/day)	NOAEL
LOXO-101-TOX-019 GLP 91 days + 28 days recovery	Cynomolgus 3+2M /3+2F	0, 10, 30, 100	NOAEL: 100 mg/kg

Mortality: None

Clinical signs: increased incidence of emesis (M 100 mg/kg), on day 2, transient decreases in blood pressure (M ≥30 mg/kg)

Body weight: higher body weight gain (M 100 mg(kg)

Hematology: decrease in red blood cell count (F 100 mg/kg),

Clinical chemistry: decreased haemoglobin, haematocrit, albumin (≥30 mg/kg). in hepatic microsomal fractions increased activity of CYP2B and CYP3A (F 100 mg/kg)

Organ weights: increased liver weight (≥30 mg/kg)

Histopathology: increased vacuolation of hepatocyte (≥30 mg/kg), increased incidence of macrovesicular change of brown fat

Recovery: all findings fully reversible, except increased CYP1A activity in females

Table 14: Summary of the Mean Larotrectinib Cmax and AUC0-24 in Monkey Plasma

Interval (Day)	Dose Group	Dose Level (mg/kg/day)	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)
1	2	10	1000	2940
	3	30	7760	21900
	4	100	32500	158000
46	2	10	898	2730
	3	30	3180	12200
	4	100	16000	70600
91	2	10	740	2620
	3	30	6400	18100
	4	100	16400	73700

Genotoxicity

Table 15: Overview of genotoxicity studies

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria/ LOXO-101-TOX-010/ GLP*	*Salmonella* strains TA1535, TA1537, TA98, and TA100, *E coli* WP2*uvr*A	Up to 5000 µg/plate+/- S9	Negative
Gene mutations in mammalian cells/ LOXO-101-TOX-010/GLP*	L5178Y/TK-/- mouse lymphoma	Up to 720 µg /ml (+/-S9)	Negative

Chromosomal aberrations in vivo/ LOXO-101-TOX-011/GLP	Mouse, micronuclei in bone marrow	Up to 500 mg/kg	Negative

***** The formulation and stability analyses were not conducted under GLP regulations but were conducted in substantial compliance with GMP regulations.

Carcinogenicity

No carcinogenicity studies have been submitted (See discussion on non-clinical aspects).

Reproduction Toxicity

Fertility and early embryonic development

Effects on reproductive organs in adult animals were assessed in the repeat dose toxicity studies. In the 4w SD rat study, there was a reversible 15-21% reduction in uterine weight in females from the lowest dose (10mg/kg BID) to the highest (100mg/kg BID), with some of the high dose females demonstrating uterine atrophy. In the 13w rat study, male rats demonstrated a reduction in prostate weight compared to body weight at 25 and 75mg/kg BID but otherwise no effects on any male reproductive endpoints (sperm count, density, motility, morphology). There were no uterine weight effects in 13w female rats making the interpretation of the 4w effects uncertain.

Effects on reproductive performance and early embryofoetal development were assessed within a GLP repeat-dose study conducted in juvenile rats with oral BID administration of larotrectinib from PND7 to 70 (see below). Mating was initiated in a subset of animals after 28-days of recovery on PND 99. Laparohysterectomy was performed on GD 15. Doses were 0.2, 2, and 7.5 mg/kg/dose BID during PND 7 to 27 and 0.6, 6, and 22.5 mg/kg/dose BID during PND 28 to 70. Lower fertility, male copulation and female conception indices as well as lower number of litters per group were observed at mid and high doses. This was not considered related to treatment by the applicant.

Embryo-foetal development

Table 16: Pivotal study: A Twice Daily Oral (Gavage) Embryo/Fetal Development Study with Larotrectinib in Rats (GLP)

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg)	NOAEL
LOXO-101-TOX-024 GLP Treatment GD 6-17	Rat (SD) 22 pregnant F	0, 10, 40, 120 (BID)	40 mg/kg (maternal) 120 mg/kg (embryofetal)

Maternal mortality: Three (3) max dose females plus 1 max dose TK female were euthanized in extremis during GD 12–17 due to poor clinical condition, including adverse observations of rales, laboured respiration, and gasping at the daily examinations and post-dosing observations.

Maternal clinical signs: The max dose females displayed rales, gasping, laboured respiration, ataxia, piloerection and head tilt, pale or cool body. An increased incidence of scabbing on various body surfaces was observed at all doses.

Maternal body weight: There was an increase in body weight and weight gain and food consumption across all doses from GD9 and until GD18.

Table 17: Pivotal study: A Twice Daily Oral (Gavage) Embryo/Fetal Development Study with Larotrectinib in New Zealand White Rabbits (GLP)

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg)	NOAEL
LOXO-101-TOX-028 GLP Treatment GD 7-20	Rabbit (NZW) 22 pregnant F +4 animals/group for TK	0, 15, 30, 75 (BID)	30 mg/kg (maternal) 75 mg/kg (embryofetal)

Maternal mortality: Two max dose (75mg/kg BID) animals were euthanized in extremis on GD11 and GD22. One was euthanized due to findings that included: impaired use of a hindlimb and fractured tibia (no signs of teratogenesis in implantations). The other was euthanized due to ataxia, prostration, body weight loss, and decrease in food consumption.

Maternal clinical signs: In the max dose (75 mg/kg BID) there was impaired use of the right hindlimb, ataxia, prostrate body, decreased defecation, and tremors upon handling. With 30 mg/kg BID, there was tremors upon handling, ataxia, and impaired use of the right hindlimb, were noted approximately 2 hours following dose administration; however, the applicant did not consider those adverse because they did not persist to the daily examinations the following day.

Maternal body weight: At all doses in the pregnant animals (≥15mg/kg BID): increased body weight gain and food consumption from GD14 until GD24. The most extensive increase in weight gain was between GD7 and GD21.

Foetal findings: Intrauterine growth, survival and foetal morphology (external, visceral, and skeletal) were unaffected by treatment with larotrectinib.

Prenatal and postnatal development, including maternal function

No pre-natal and postnatal development, including maternal function studies have been submitted.

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

In order to support the twice daily oral administration of larotrectinib as a monotherapy for paediatric patients ranging in age from 1 month to 12 years, with advanced cancer, two dose DRF studies and a GLP repeat-dose oral toxicity study in juvenile rats were conducted. In the pivotal study, larotrectinib was administered via oral gavage from PND 7 to PND 70 followed by a 28-day recovery period. A subset of animals was assigned for the assessment of the reproductive potential with mating initiated 28 days after end of dosing on PND 99. In the females, laparohysterectomies were performed on GD 15. Doses investigated were 0, 0.4, 4 or 15 mg/kg/day from PND 7 to PND 27. From PND 28 to PND 70 the doses were increased to 1.2, 12 or 45 mg/kg/day to adjust for lower exposures on PND 28.

Table 18: summary of juvenile toxicity studies conducted with larotrectinib

Species Study no. GLP	Duration, route, doses	Major findings
Rat (SD) (main:10/sex/group; TK: 36/sex/group) LOXO-101-TOX-020 GLP: no	PND 7-28 Oral (gavage) 0, 30/30, 100/1, 200/3, 300/10 mg/kg/day* (0, 15/15, 50/0.5, 100/1.5, 150/5.0 mg/kg BID*)	*Endpoints: survival, clinical observations, body weights, gross pathology, TK* • ≥30: **mortality** (n=15, 21, 10, 27 main+TK pups from PND 7-17 – of these, 0, 8, 5, 15 died before lowering the dosage levels), **clin. signs** (head flick and partial closure of the eyes on PND 20-29, swollen abdomen), **↓BWG** • ≥100/1: **clin. signs** (cool/pale body, hypoactivity, thinness), **BW loss**
Rat (SD) (main:10/sex/group; TK: 36/sex/group) LOXO-101-TOX-022 GLP: no	PND 7-28 Oral (gavage) 0, 2, 6, 20 mg/kg/day (0, 1, 3, 10 mg/kg BID)	*Endpoints: survival, clinical observations, body weights, clinical pathology, gross pathology, organ weights, histopathological examination (21 organ/tissues), TK* • ≥LD: **hemato.** (↓reticulocytes), **lungs** (↓wt correlating with reduced inflation and emphysema), **kidneys** (interstitial fibrosis) • ≥MD: **mortality** (TK animals on PND14-17: 1F at MD and 2M at HD), **clin. signs** (partially closed eyes, thin bodies, swollen abdomen), **↓BWG and BW**, **hemato**. (↓RBC count, Hb, Ht), **biochem.** (↓total protein, globulin, calcium, albumin), **kidneys** (↓wt, tubular degeneration)
Rat (SD) (main:45/sex/group**; TK: 33/sex/group) LOXO-101-TOX-021 GLP: yes	PND 7-70 Oral (gavage) Doses: – PND 7-27: 0, 0.4, 4, 15 mg/kg/day (0.2, 2, 7.5 mg/kg BID) – PND 28-70: 0, 1.2, 12, 45 mg/kg/day (0, 0.6, 6, 22.5 mg/kg BID)	*Endpoints: survival, clinical observations, body weights, food consumption, onset of puberty, auditory startle response (PND60 and 85), FOB assessments (PND61 and 86), motor activity (PND61 and 86), Biel maze swimming test (PND62 and 87), ophthalmic examination (PND66-70), reproductive performance (estrous cycle assessment for 14 days followed by mating at PND≥100), spermatogenic assessment (motility, morphology, count, production rate), clinical pathology, terminal procedures (incl. organ wt, femur length, histopathology), TK* • **Mortality**: 4M+3F on PND9-16 at HD, cause not determined • **Clinical signs:** partial/complete closure of eyes at ≥MD persisting during recovery; transient head flick and circling, swollen abdomen, scabbing on various body areas at HD • **BW/FC:** ↓BWG and FC on PND7-28 at MD; ↓BWG/BW in M correlating with ↓FC in M at HD (not reversible), ↓BWG and FC on PND7-28 in F at HD (followed by ↑ on PND28-70) • **Tibial length:** ↓ in M from PND49-52 at MD; ↓ at HD from PND14-52 • **Sexual maturation:** delayed in M at ≥MD and in F at HD in relation to the effects on BW • **FOB** ✓ Home cage and handling observations: ↑ incidence of slightly drooping, half-closed or completely shut eyelids at HD (PND61 and 86) ✓ Neuromusclar effects: ↓ hindlimb gripstrength at HD (PND61), ↓ hindlimb footsplay values in M at ≥MD (PND61+86) and in F at HD (PND61) • **Motor activity:** ↑ mean total and ambulatory counts in M at ≥MD on PND61 due to effects during the first 3-4 intervals (no effect on PND86); ↑ mean total counts in F at ≥MD on PND86, no effect on ambulatory counts • **Reproduction:** ↓ indices for male and female fertility, male copulation, and female conception at HD vs. study controls but within historical control range • **Biochemistry:** ↑BUN, creatinine, and phosphorus at ≥MD on PND71 (not fully reversed in HD males on PND99); ↑ASAT at ≥MD on PND71 (not fully reversed in HD males on PND99) • **Hematology:** ↓RBC count, Hb, Ht at ≥MD • **Organ weights:** ↑ heart, liver, spleen wt on PND71 (resolved for heart and liver, and partially resolved for spleen on PND99)

Toxicokinetic data

See section on repeat dose toxicity.

Local Tolerance

Local tolerance of the larotrectinib formulations has not been performed since the clinical route of administration is oral.

Other toxicity studies

Antigenicity

No studies were performed as larotrectinib is a small molecule. No signs for antigenicity were seen in repeat-dose toxicity studies in rat and monkey

Immunotoxicity

Effects on the immune system were assessed within repeat-dose toxicity studies in rat and monkey. No separate studies conducted according to ICH-S9.

Dependence

No relevant off-target effects on a range of targets and receptors were seen. Dependence to larotrectinib is therefore not likely and no studies were conducted.

Metabolites

The O-glucuronide metabolite M14 identified as a major human metabolite does not raise any specific concerns. It is regarded as qualified since it is present in plasma of monkey and rat. No other unique or relevant disproportionate human metabolites were identified. No dedicated toxicology studies on metabolites were therefore conducted.

Studies on impurities

Drug substance used in non-clinical safety studies was produced by a process representative of production of clinical batches with a similar impurity profile, and specified impurities are therefore regarded as toxicologically qualified. No dedicated toxicology studies on impurities were conducted.

Phototoxicity

The phototoxic potential of larotrectinib was assess in vitro in BALB/c 3T3 mouse fibroblasts (LOXO-101-TOX-017). Larotrectinib did not demonstrate a phototoxic potential in this assay.

2.3.5. Ecotoxicity/environmental risk assessment

Larotrectinib (CAS #1223405-08-0) has the chemical formula $C_{21}H_{24}F_2N_6O_6S$ and a molecular weight of 526.52g/mol. Larotrectinib is slightly water soluble at 3.6mg/mL at pH3.7 and ~2mg/mL at pH≥7.8. From a 100 mg single oral dose in the clinical trials, ~13% and ~7% of larotrectinib was recovered as unchanged compound in urine and faeces respectively. Detected metabolites were mostly in the form of glucuronide conjugates. The n-octanol/water partition coefficient (log K_{OW}) submitted for larotrectinib was inadequate. A surface water predicted environmental concentration (PEC_{SW}) was calculated based on a, by the applicant stated number of patients in the EU with the propose indication (i.e. NTRK positive tumours; n=40,363) giving a PEC_{SW} of 0.0079ug/L.

Table 19: Summary of main study results

Substance (INN/Invented Name): Larotrectinib					
CAS-number (if available): #1223405-08-0					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107				Potential PBT (Y/N) Experimental log Kow study requested
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				B/not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0079 ug/L	µg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	NA
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	NA
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	NA
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			NA
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	NA
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	NA
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	NA
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	NA
Sediment dwelling organism		NOEC		mg/kg	NA

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

The applicant is recommended to conduct a new study on octanol/water partitioning according to OECD technical guidelines (e.g. OECD TG107). The study report and the updated ERA will be available by 20 December 2019.

2.3.6. Discussion on non-clinical aspects

Pharmacology

This application represents a novel approach for cancer treatment in that the proposed indication is only based on a tumour biomarker, the presence of a TRK gene fusion irrespective of the histological origin of the tumour. TRK gene fusions tumours are relatively rare, so in the clinical program supporting this application some tumour forms are very poorly represented. NTRK fusion tumours are rare and only a very limited number of cell lines harbouring NTRK fusions are described in the literature.

While the pharmacokinetic program provides evidence that the animal models are relevant with regard to metabolism, there exists a deficiency in the documentation on the activity of larotrectinib on TRKA, TRKB and TRKC in the animal species used for safety evaluation. The applicant has not provided data on the activity of larotrectinib on TRK from toxicology species. However, sequence alignment shows a high degree of homology between kinase domain from rat, mouse rabbit monkey and human. Key residues for binding to larotrectinib, identified from the co-crystal structure of the kinase domain of TRKA in complex with larotrectinib, showed 100 % homology between species. A pharmacological relevance of the non-clinical animal studies is further supported by the finding of weight gain seen consistently across species as well as transient, CNS findings described primarily in juvenile rats. Taken together, it is agreed that the species chosen are regarded as appropriate to assess not only off-target but also target-related, primary pharmacodynamics effects of larotrectinib.

Although the nonclinical data package is limited to a small number of TRK fusion cell lines, the data are considered to be fully compatible with a tissue-independent activity, involving TRKA, TRKB and TRKC. The extrapolation to all tumours with TRK fusions must be based on clinical data. It is still considered of importance to acquire further understanding on the tumour biology of the TRK fusion tumours and the activity of larotrectinib, particularly in relation to primary and secondary resistance. Such exploratory analysis should be part of the clinical study(ies) performed as post-approval measures for a conditional marketing approval (see Clinical part of the AR).

Pharmacokinetics

The nonclinical pharmacokinetics of larotrectinib is adequately evaluated. It can be noted that there was a lack of larotrectinib distribution to some rat tissues that are considered relevant for NTRK positive tumours (e.g. liposarcoma, osteosarcoma, ocular cancer or cerebral tumours) but this may be due to insufficient sensitivity of the methodology (i.e. <LLOQ in the QBWA study). Of importance for the safety evaluation are the observations that the distribution studies show a limited distribution to the brain. These studies also show that transporters such as Mdr1a, Mdr1b and Bcrp contribute to the low CNS penetration. Since the TRKs are of importance for CNS function, the low distribution to the brain may contribute to the safety by limiting pharmacological activity in the adult rodent CNS. The limited distribution to the brain is also of importance for the clinical efficacy evaluation for treatment of CNS tumours (see discussion on clinical efficacy). What is less clear, and of relevance considering the results

from the juvenile toxicity study, is the extent of the distribution to the postnatal and juvenile CNS (see Toxicology section below).

Toxicology

With regard to the toxicological aspects, there were several animal deaths in the 28 and 91-day repeat-dose toxicity studies. For the 91-day repeat-dose study, deaths are mostly attributed to multiple severe skin lesions and inflammation. No clear causes of mortality/moribund conditions were determined for the 28d animals. Rats in general demonstrated an unusual skin lesion effect (also seen in the rat juvenile toxicity study). No similar skin findings were seen in monkeys nor have there been indications on a similar human effect from the clinical trial data. This would indicate them to be rat species specific effects. Overall, there were no findings in the repeat-dose toxicity studies that are considered of importance for the benefit-risk assessment in the proposed indication or requiring further risk mitigation in the clinic.

Clinical signs of gastrointestinal toxicity were dose limiting in monkeys. In rats, severe toxicity (STD10) was observed at doses corresponding to 1 to 2 times the human AUC at the recommended clinical dose. No relevant systemic toxicity was observed in monkeys at doses which correspond to > 10 times the human AUC at the recommended clinical dose (see section 5.3 of the SmPC).

Pre-weaning animals (in particular PND9-16) were found to be more sensitive than post-weaning animals (i.e. post PND28). There is no clear explanation for this effect and no clear indication on the subject is provided by the clinical safety data. A clinical effect on body weight in infants cannot therefore be excluded and patients will therefore be monitored accordingly. Body weight gain was decreased in pre weaning male and female pups, with a post weaning increase in females at the end of exposure whereas reduced body weight gain was seen in males also post weaning without recovery. Based on the mechanism of action, foetal harm cannot be excluded when administering larotrectinib to a pregnant woman. Women of childbearing potential should have a pregnancy test prior to starting treatment with larotrectinib. Women of childbearing potential must use highly effective contraception while taking larotrectinib and for at least one month after stopping treatment (see sections 4.5 and 4.6).

Males of reproductive potential with a non-pregnant woman partner of child bearing potential should be advised to use highly effective contraception during treatment with larotrectinib and for at least one month after the final dose (see section 4.4 and 4.6 of the SmPC).

Larotrectinib was not teratogenic and embryotoxic when dosed daily during the period of organogenesis to pregnant rats and rabbits at maternotoxic doses, i.e. corresponding to 32-times (rats) and 16-times (rabbits) the human AUC at the recommended clinical dose. Larotrectinib crosses the placenta in both species (see section 5.3 of the SmPC).

Overall, preclinical literature data indicate that intact TRK signalling is relevant for both prenatal and postnatal brain development and has an important role in synaptic plasticity.

In the juvenile toxicity studies, there was a 2-2.5d delay in sexual maturation landmarks for both sexes (balanopreputial separation in males, vaginal patency in females). These effects may or may not be linked to the early growth retardation recorded in both sexes (i.e. pre-PND28). A developmental growth retardation connection to sexual maturity seems reasonable for males but as females experienced a boost in weight gain after PND28, the delay in vaginal patency may be either a consequence of the earlier growth retardation and/or due to a sex-specific post PND28 response. The same issue can be noted for the reduction in tibia length recorded in both males and females between PND14 and 52 at the high dose. Pre weaning mortality (before PND 21) was observed at the high dose level corresponding to 2.5 to 4 times the AUC at the recommended dose.

Nervous system effects (i.e. altered hindlimb functionality and, likely, increases in eyelid closure) demonstrated partial recovery. Regarding the observed juvenile eye lid effects that remained during the recovery period, the underlying reasons remain unclear. The toxicokinetic data indicates a somewhat negative dose accumulation until PND70 so there is likely less of a systemic exposure on PND86. Overall, it seems likely that the eye lid effects have a neural basis. Together with the observed increase in total activity and impairment of hindlimb motoric function (an effect that may relate to the hindlimb effects seen at high dose in pregnant rabbits) which also remained during recovery, there is reason to believe that larotrectinib induces neural (possibly long lasting) effects in juvenile animals. It can be noted that the non-clinical pharmacokinetics studies did only find limited distribution of larotrectinib to the adult rodent central nervous system but it remains unclear how the distribution profile is in juvenile rats. Overall, the juvenile toxicity study in rats demonstrated that postnatal larotrectinib exposed pups are especially sensitive to exposure and also identified several endpoints concerning both developmental growth and behaviour starting from 2/6mg/kg BID. No satisfactory explanation has been provided for the observations of hindlimb effects and eyelid effects still remaining in the recovery period and while it can be argued that the early 'brain exposure' is likely greater in rodents than in humans due to the early exposure initiation of PND7, this does not negate the uncertainty that also later (i.e. post PND14 or PND21) exposure periods may generate neurodevelopmental effects at lower 'brain exposure' (especially considering the absence of any systemic exposure margin).

Fertility studies with larotrectinib have not been conducted. No effects on female reproductive organs were seen in the 3 months toxicity studies in rats and monkeys at doses corresponding to approximately 3 times (female rats) and 17 times (female monkeys) the human AUC at the recommended clinical dose. A decrease in pregnancy rate was also reported despite normal mating at the high dose level. In 3 months toxicity studies, larotrectinib had no histological effect on the male reproductive organs in rats and monkeys at the highest tested doses corresponding to approximately 7 times (male rats) and 10 times (male monkeys) the human AUC at the recommended clinical dose. In addition, larotrectinib had no effect on spermatogenesis in rats (see section 5.3 of the SmPC). No effects on F1 offspring development were seen.

Growth and nervous system effects were seen at 0.5 to 4 times the AUC at the recommended dose.

Carcinogenicity studies have not been performed with larotrectinib. Larotrectinib was not mutagenic in bacterial reverse mutation (Ames) assays and in *in vitro* mammalian mutagenesis assays. Larotrectinib was negative in the *in vivo* mouse micronucleus test at the maximum tolerated dose of 500 mg/kg (see section 5.3 of the SmPC).

Environmental risk assessment

The Phase I assessment of the ERA for Vitrakvi/larotrectinib by the applicant was based on a proposed maximum daily dose of 200mg/kg and, after calculating a refined prevalence Fpen using all eligible tumour forms as stated in the Risk Management Plan (RMP), a market penetration factor (Fpen) of 0.0079%. This gives a Phase I PEC_{SW} of 0.0079ug/L which is below the action threshold for Phase II assessment (0.01ug/L). The prevalence estimate was based on population frequency estimates for NTRK positive tumours for different tumour forms described in different academic articles - giving a 5 year prevalence estimate of 40363 patients (data not shown). The presently included log Kow study (giving a Log K_{OW} value between 0.67 and 1.85) is of insufficient quality. As a consequence, the available data does not allow concluding definitively on the potential risk of larotrectinib to the environment. The applicant is recommended to conduct a new study on octanol/water partitioning according to OECD technical guidelines (e.g. OECD TG107). The study report and the updated ERA will be available by 20 December 2019.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data package submitted to support this application is acceptable.

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

Clinical pharmacokinetic and pharmacodynamic data were retrieved from the clinical studies described in (Table 20, Table 21 and Table 22). A brief description of the study design and a summary of the pharmacokinetic results are included in the tables.

Table 20: Summary of Clinical Pharmacology Studies

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects / Type (#M / #F) (Age Range)	Arithmetic mean ± SD or median (range)			
					C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng*h/mL)	$t_{1/2}$ (h)
LOXO-TRK-16007	Food/ formulation effect	Cross-Over	100-mg (One 100-mg Capsule, Oral), Fasted Reference [DP-APS15-111-A]	18 HV (12 M/6 F) (26-54 years)	553 ± 231	0.76 (0.46– 2.00)	1345 ± 511	4.13 ± 2.30
			100-mg (One 100-mg Capsule, Oral) Fed [DP-APS15-111-A]	17 HV (11 M/6 F) (26-54 years)	339 ± 96	3.00 (2.00–4.08)	1436 ± 621	5.04 ± 2.42
			100-mg (5 mL 20-mg/mL Solution, Oral), Fasted [16-0035]	17 HV (11 M/6 F) (26-54 years)	741 ± 314	0.44 (0.21–1.01)	1393 ± 532	5.59 ± 3.77
LOXO-TRK-16009	Ascending dose	Parallel	100-mg (One 100-mg Capsule, Oral), Fasted [DP-APS16-101-A]	6 HV (4 M/2 F) (22-51 years)	554 ± 433	1.05 (0.56–2.05)	1623 ± 671	3.43 ± 0.983
			200-mg (Two 100-mg Capsules, Oral), Fasted [DP-APS16-101-A]	6 HV (4 M/2 F) (25-54 years)	1183 ± 491	1.05 (0.55–2.06)	3017 ± 1533	4.11 ± 2.50
			400-mg (Four 100-mg Capsules, Oral), Fasted [DP-APS16-101-A]	6 HV (3 M/3 F) (21-48 years)	2550 ± 1225	0.81 (0.55–1.07)	7074 ± 2533	3.64 ± 0.72
			600-mg (Six 100-mg Capsules, Oral), Fasted [DP-APS16-101-A]	6 HV (2 M/4 F) (23-51 years)	4868 ± 1972	1.06 (1.05–1.55)	17150 ± 4544	3.28 ± 0.32
			700-mg (Seven 100-mg Capsules, Oral), Fasted [DP-APS16-101-A]	6 HV (3 M/3 F) (42-55 years)	4708 ± 1076	1.05 (1.05–1.57)	18980 ± 2707	3.20 ± 0.91
			900-mg (Nine 100-mg Capsules, Oral), Fasted [DP-APS16-101-A]	6 HV (3 M/3 F) (27-54 years)	7437 ± 2430	1.08 (0.56-2.06)	25170 ± 8923	2.84 ± 0.47

LOXO-TRK-16011	Absolute bioavailability	Simul-taneous	100-mg (One 100-mg Capsule, Oral), Fasted [DP-APS16-101-A]	6 HV (6 M) (22-50 years)	445 ± 184	0.71 (0.50–1.03)	1090 ± 469	2.91 ± 1.52
			7.58-µg (Solution (^{14}C), IV, Fasted) [9513AXU003-28]		0.341 ± 0.185	0.0333 (0.0333, 0.167)	0.231 ± 0.0903	1.38 ± 0.11
	Metabolism	Single-Dose	100-mg (5 mL 20-mg/mL Solution, Oral), Fasted [16-0035, 9513AXU003-28 (^{14}C)]	6 HV (6 M) (18-52 years)	569 ± 190	0.50 (0.50–0.53)	1000 ± 340	2.93 ± 2.70
LOXO-TRK-16013	Hepatic impairment	Single dose	100-mg (One 100-mg Capsule, Oral), Fasted [DP-APS16-101-A, DP-APS17-133-A]	11 HV (7 M/4 F) (49–65 years)	564 ± 222	0.50 (0.42–2.00)	1200 ± 478	5.39 ± 5.12
				8 (5 M/3 F) (50–64 years) with mild hepatic impairment	579 ± 119	1.00 (0.50–1.03	1410 ± 222	8.19 ± 4.63
				8 (7 M/1 F) (49–65 years) with moderate hepatic impairment	679 ± 198	1.00 (0.50–2.00	2460 ± 902	8.13 ± 3.61
				8 (6 M/2 F) (48–62 years) with severe hepatic impairment	893 ± 452	0.50 (0.50–3.00)	3800 ± 1690	7.92 ± 3.31
LOXO-TRK-17014	Renal impairment	Single dose	100-mg (One 100-mg Capsule, Oral), Fasted [DP-APS17-127-A]	8 ESRD (7 M/1 F) (40-61 years)	627 ± 381	1.00 (0.5–2.0)	2076 ± 1369	7.16 ± 5.36
				8 HV (7 M/1 F) (43-60 years)	470 ± 190	0.75 (0.5–3.0)	1248 ± 353	6.35 ± 3.31

Table 21. Summary of Drug Interaction Studies

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects / Type (#M / #F) (Age Range)	Arithmetic Mean ± SD or median (range)				Mean ratio (%) Confidence interval	
					C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng*h/mL)	$t_{1/2}$ (h)	C_{max}	AUC_{0-t}
LOXO-TRK-16010	DDI: multiple dose of itraconazole and rifampin on single dose larotrectinib	Fixed sequ--ence	100 mg larotrectinib (One 100-mg Capsule, Oral), Fasted [DP-APS16-101-A]	12 HV (6 M/6 F) (20-55 years)	529 ± 187	1.00 (0.5–1.01)	1324 ± 440	5.59 ± 3.60		
			200 mg itraconazole QD from Day -4 to Day 3 with single dose 100 mg larotrectinib on Day 1		1434 ± 352	1.00 (1.00–2.99)	5518 ± 640	11.19 ± 4.31	281 (226, 349)	433 (377, 498)
			100 mg larotrectinib (One 100-mg Capsule, Oral), Fasted [DP-APS16-101-A]	12 HV (8 M/4 F) (21-54 years)	510 ± 289	1.00 (0.50–2.05	1489 ± 837	5.16 ± 4.22		
			600 mg rifampin QD from Day 1 to Day 11 with a single dose 100 mg larotrectinib on Day 1		843 ± 220	1.00 (0.50–1.00)	2354 ± 899	1.99 ± 0.40	179 (147, 219)	168 (153, 185)
			and a single dose 100 mg larotrectinib Day 10		146 ± 59	0.50 (0.34–2.00)	267 ± 81	1.44 ± 0.65	29 (23, 37)	19 (16, 24)
LOXO-TRK-16012	DDI: multiple dose larotrectinib on single dose midazolam	Fixed sequ-ence	Single oral dose 2 mg midazolam on Day 1	16 HV (15M/1F) (21-51 years)	9.5 ± 3.5	0.52 (0.50–1.00)	25.0 ± 11.3	5.52 ± 2.42		

Table 22. Description of Studies Included in the Dose-Exposure, Exposure-Response and PopPK analysis

Study Number and Conduct Dates	Location Number of Enrolling Sites	Study Design and Objectives	Larotrectinib Doses and Formulation	Total Number of Patients		
				Receiving Larotrectinib	Included in Dose-Exposure Analysis	Included in Exposure-Response Analysis
LOXO-TRK-14001 May 2014–ongoing	US 8 sites	Multicenter, Phase 1, open-label, 3 + 3 dose-escalation study in adult patients with advanced solid tumors. Objectives are to characterize safety and dose-limiting toxicity, maximum tolerated dose/or appropriate dose of larotrectinib for further study, overall response rate (CR + PR), and other efficacy parameters.	50–600 mg/day (QD or BID) Opaque white gelatin capsules of 25-mg and 100- mg strengths or oral solution	66	66	56
LOXO-TRK-15002 Sep 2015–ongoing	US, EU, Singapore 17 sites	Multicenter, Phase 2, open-label "basket" study in patients 12 years of age or older with an advanced cancer bearing an NTRK fusion. Objectives are to determine the overall response rate (CR + PR) and other efficacy parameters.	100 mg BID Opaque white gelatin capsules of 25-mg and 10-mg strengths or oral solution	47	45	40
LOXO-TRK-15003 Dec 2015–ongoing	US, EU 13 sites	Multicenter, Phase 1/2, open-label, dose-escalation study in pediatric patients with advanced solid or primary CNS tumors. Objectives are to characterize safety and dose-limiting toxicity, maximum tolerated dose/or appropriate dose of larotrectinib for further study, overall response rate (CR + PR), and other efficacy parameters.	Dosing based on adult equivalent of 100 or 150 mg BID, then 100 mg/m^2 BID (with a maximum of 100 mg BID) Capsules (25 mg and 100 mg) or oral solution	31	29	23
Total				144	140	119

BID = two times daily; CNS = central nervous system; CR = complete response; EU = European Union; NTRK = neurotrophic tyrosine receptor kinase; PR = partial response; QD = once daily; TRK = tropomyosin receptor kinase; US = United States.

The efficacy assessment is based primarily on the pooled interim data from three currently ongoing trials (Table 23). Two are dose-finding phase 1/2 studies, one in adults with advanced solid tumours with or without NTRK gene fusions (LOXO-TRK-14001), and one in paediatric patients with advanced solid tumours or primary CNS malignancies with or without NTRK gene fusions (LOXO-TRK-15003). The third is a phase 2 basket trial in adolescent and adult patients with NTRK fusions (LOXO-TRK-15002).

Table 23: Summary of clinical studies of efficacy and safety (Studies 14001, 15002, and 15003)

Study ID Number of Study Centres Locations	Study start, Enrolment status, Date Total Enrolment / Enrolment goal	Design Control Type	Study Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm entered/ completed	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Study Endpoint(s)
LOXO-TRK-14001 8 sites US	12 MAY 2014 – ongoing Data cut-off: 30 JUL 2018 61 patients (of whom 8 with NTRK fusions) in dose escalation phase, 2 in NTRK fusion and 9 in the Other (NOS) expansion phase Goal: Approximately 60 patients for the escalation phase and up to 40 patients in expansion phase	Phase 1, open-label, 3 + 3 dose escalation study with expansion phase in patients with *NTRK* gene fusions only	Larotrectinib 50–400 mg/day QD or BID in dose escalation phase Larotrectinib 100 mg BID in expansion phase Oral	Characterize safety, DLT, MTD/ or appropriate dose of larotrectin b for further study	Dose escalation: 50 mg QD 4/4 100 mg QD 5/5 100 mg BID 34/29 200 mg QD 5/5 150 mg BID 7/6 200 mg BID 6/6 Dose expansion: • NTRK fusion 100 mg BID: 2/0 • Other (NOS): 100 mg BID: 9/9 Overall: 72/64 8 patients ongoing	Treatment continued until disease progression, unacceptable toxicity, or other reason for discontinuation Patients with progressive disease could continue larotrectinib if it was providing clinical benefit.	35/37 60 years (19-82)	Adult patients with advanced solid tumours. In expansion phase, patients with *NTRK* gene fusions only	Primary endpoints: Safety, MTD and recommended dose for Phase 2. Secondary endpoints: ORR (CR + PR) Duration of response
LOXO-TRK-15002 22 sites US, EU, Singapore, South Korea	13 OCT 2015 - ongoing Data cut-off: 30 JUL 2018 82 (10, 15, 14, 6, 16, 2, 4, 14, and 1 respectively, in Cohorts 1, 2, 3, 4, 5, 6, 7, 8, and 9) Goal: Up to 18 patients per tumour specific cohort and up to 25 patients in the other histologic types or patients without measurable disease cohort.	Phase 2, open-label "basket" study	Larotrectinib 100 mg BID Oral	Determine the ORR	Non-small cell lung cancer 10/2 Thyroid 15/3 Sarcoma 14/4 Colorectal 6/5 Salivary gland 16/4 Biliary 2/2 Primary CNS 4/3 Others 14/8 No CLIA lab cert 1/0 82/31 51 patients ongoing	Treatment continued until disease progression, unacceptable toxicity, or other reason for discontinuation Patients with progressive disease could continue larotrectinib if it was providing clinical benefit	41/41 58 years (6-79)	Patients 12 years of age or older with an advanced cancer bearing an *NTRK* gene fusion	Primary endpoint: ORR (CR + PR) Secondary endpoints: Best overall response, duration of response, Clinical benefit rate, PFS, OS, Exploratory Quality of life Safety

Study ID **Number of Study Centres** **Locations**	**Study start, Enrolment status, Date** **Total Enrolment / Enrolment goal**	**Design** **Control Type**	**Study Drugs** **Dose, Route & Regimen**	**Study Objective**	**No. of Subjects by Arm entered/ completed**	**Duration**	**Gender M/F** **Median Age (Range)**	**Diagnosis** **Inclusion Criteria**	**Study Endpoint(s)**
LOXO-TRK-15003 17 sites US, EU, Australia	16 DEC 2015 - ongoing Data cut-off 30 JUL 2018 24 dose escalation 5 Phase 1 expansion 25 Phase 2 (of which 45 patients with NTRK fusion cancer) Goal: Phase 1 dose escalation up to 36 patients Phase 1 expansion: up to 18 patients Phase 2: approximately 10 patients in each of the following cohorts: 1. IFS, 2. other extracranial solid tumours, and 3. primary CNS tumours	Phase 1, open-label, dose escalation study Phase 2, single arm open-label study in IFS, other extracranial solid tumours, and primary CNS tumours	Larotrectinib Dosing based on adult equivalent of 100 or 150 mg BID, then 100 mg/m^2 BID (maximum of 100 mg BID) Oral	Characterize safety and DLT, MTD/ or appropriate dose of larotrectin b for further study	Cohort 1: 4/2 (9.6-55.0 mg/m^2) Cohort 2: 11/6 (17.3-120.0 mg/m^2) Cohort 3: 39/12 (100 mg/m^2 BID, with a maximum of 100 mg BID) 54/20 34 ongoing	Treatment continued until disease progression, unacceptable toxicity, or other reason for discontinuation Patients with progressive disease could continue larotrectinib if it was providing clinical benefit	26/28 5.0 years (0.1-19.9)	Paediatric patients 1 month to <21 years of age with advanced solid or primary CNS tumours	Phase 1 Primary endpoint Safety, DLT Secondary endpoints: Best overall response, Duration of response Quality of life Safety Phase 2 Primary endpoint ORR (CR + PR) Secondary endpoints Duration of response Safety

Abbreviations: BID = twice daily; CNS = central nervous system; CR = complete response; DLT = dose limiting toxicity; EU = European Union; IFS = infantile fibrosarcoma; MTD = maximum tolerated dose; *NTRK* = neurotrophic tyrosine kinase receptor gene; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; QD = once daily; US = United States of America

2.4.2. Pharmacokinetics

The clinical pharmacology studies of larotrectinib in healthy volunteers included a multiple ascending dose study, a food and formulation effect study, a mass balance study, a PK study in subjects with renal impairment, a PK study in subjects with hepatic impairment and two drug-drug interactions studies (Table 20 and Table 21). In these studies, larotrectinib was administered as single 100 mg dose or as repeated 100 mg twice daily for 10 days, except in study LOXO-TRK-16009 where single doses up to 900 mg were administered.

A population-PK analysis, an exposure-response as well as QTc modelling is also provided. In addition, a full in vitro package characterising in vitro metabolism, transporters, protein binding as well as potential to inhibit or induce enzymes or transporters is provided.

The proposed indication includes children in all ages, and the paediatric dose has been chosen aiming to give a similar larotrectinib exposure as in the adult population.

Methods

- *Bioanalysis*

Plasma and urine concentrations of larotrectinib were determined with LC-MS/MS methods.

- *Non-compartment data analysis*

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

- *Population pharmacokinetic analysis*

Plasma concentration from the clinical trials LOXO-TRK-16007 and LOXO-TRK-16012 (healthy subjects, full PK profiles) and LOXO-TRK-14001 (dose escalating phase I in solid tumours, 50 mg QD to 200 mg BID, full PK profiles on day 1), LOXO-TRK-15002 (phase II basket trial, 100 mgx2, sparse sampling), and LOXO-TRK15003 (dose escalation + expansion, paediatric patients, full profiles cycle 1 and one additional cycle) were included in the popPK analysis.

All samples below the BQL were set to zero. The dataset consisted of 3287 valid larotrectinib concentration measurements from 240 subjects (34 healthy subjects and 206 patients whereof 58 patients were from the study LOXO-TRK-15003).

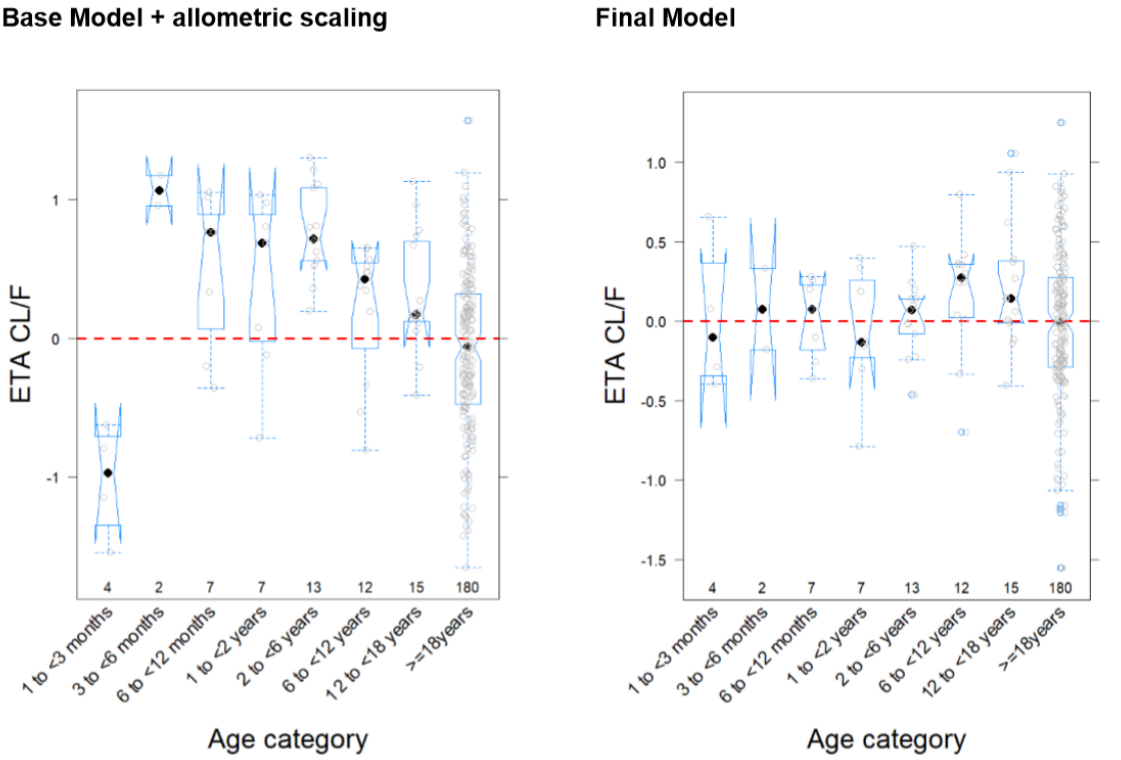
Table 24: Summary of the number of subjects in each Age Category of PK Analysis Subjects

Categorical Covariate	Value	Healthy Subjects (N=34)	Patients (N=206)	Overall (N=240)
Age Group	1 to <3 months	0 (0%)	4 (1.9%)	4 (1.7%)
	3 to <6 months	0 (0%)	2 (1%)	2 (0.8%)
	6 to <12 months	0 (0%)	7 (3.4%)	7 (2.9%)
	12 months to <2 years	0 (0%)	7 (3.4%)	7 (2.9%)
	2 to <6 years	0 (0%)	13 (6.3%)	13 (5.4%)
	6 to <12 years	0 (0%)	12 (5.8%)	12 (5.0%)
	12 to <18 years	0 (0%)	15 (7.3%)	15 (6.2%)
	≥18 years	34 (100%)	146 (70.9%)	180 (75.0%)

A two-compartment model with first order absorption and first order elimination was developed to describe the larotrectinib pharmacokinetics. A proportional error model was used to describe residual variability.

The covariates of interest included weight (kg), BSA (m2), age, age category (1-3 months, 3-6 months, 6-12 months, 1-2 years, 2-6 years, 6-12 years, and >12 years) sex, race, ethnicity, patient status (healthy volunteer or patient), baseline renal and hepatic functions (CRCL, SCR, ALB, BILI, AST, ALT, ALP). An initial screening of covariates was made graphically. Only BSA and weight appeared to correlate to Cl/F and V2/F. Weight was chosen as the preferred covariate. Fixed allometric scaling was used to describe the covariate relationship, using an exponent of 0.75 for clearance parameters and an exponent of 1 for volume parameters.

A plot of the eta CL/F values versus age and age category showed a large deviation for the youngest age group (Figure 7). To describe the age difference either (1) a maturation function based on post-natal age or (2) combinations of the categorical age groups specified in the analysis plan. The model that successfully minimized with the lowest objective function value included an age category effect on CL/F with 3 distinct age groups (<3 months, ≥3 months to <6 years, and ≥6 years) rather than a maturation function.



CL/F=apparent clearance.
Note: The circles represent individual data points, the red dashed line represents the population prediction (ETA=0), the blue box represents the interquartile range, and the whiskers represent the minimum and maximum values.

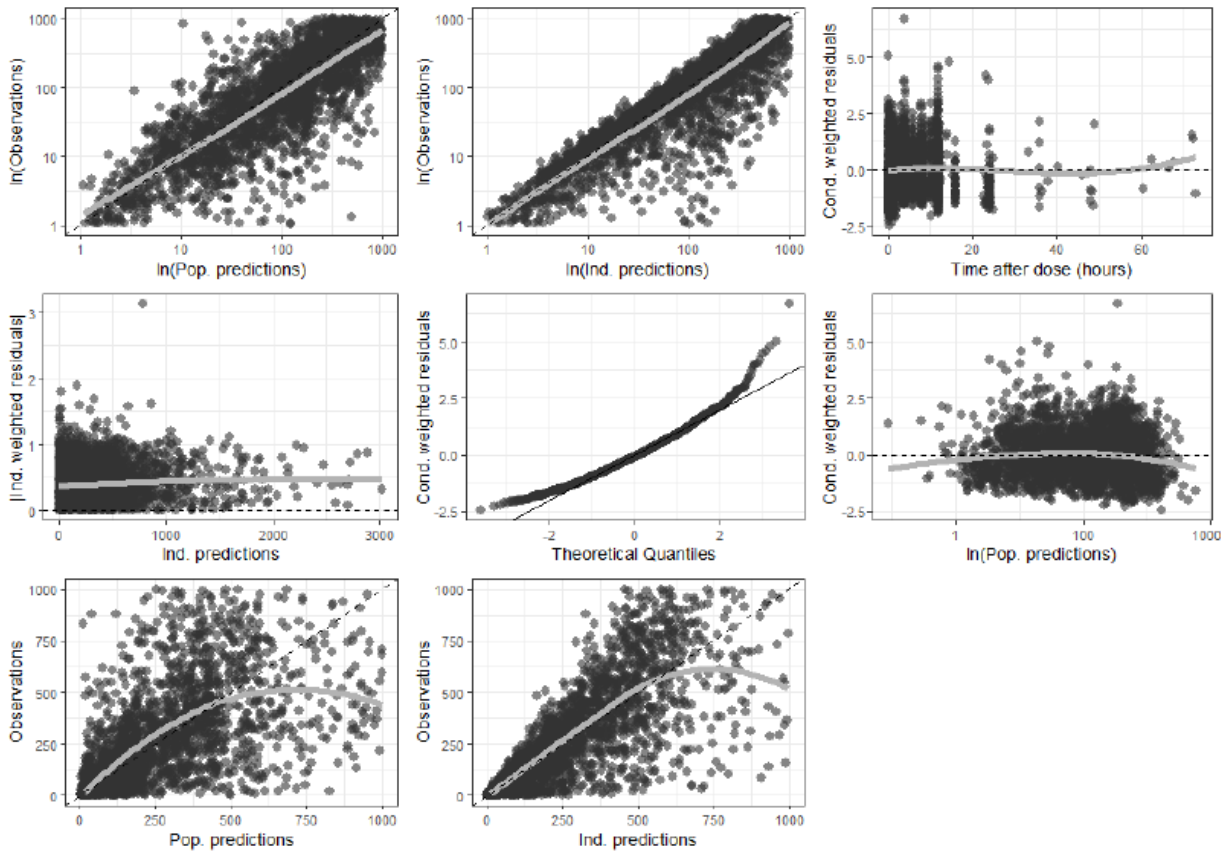
Figure 8: Plot of ETA CL/F Values versus Age Categories

The final parameter estimates are presented in Table 25.

Table 25: Parameter estimates for the Final Population PK Model for Larotrectinib

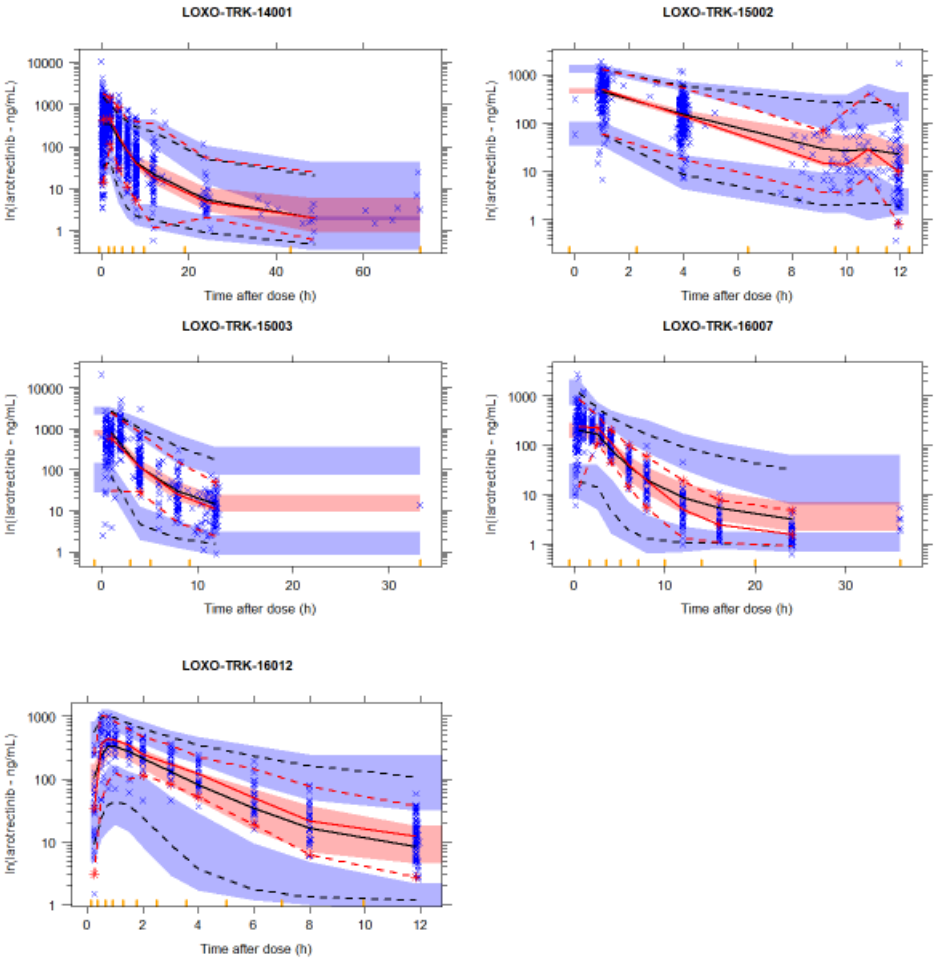
Parameter	Estimate	95% CI	RSE (%)	Shrinkage (%)
Ka (1/h)	5.28	[4.51-6.05]	7.4	—
CL/F (L/h) - 6 years and older	56.2	[50.9-61.5]	4.8	—
Vc/F (L)	141	[131-152]	3.8	—
Vp/F (L)	88.6	[70.3-107]	11	—
Q/F (L/h)	6.18	[5.16-7.19]	8.4	—
Dur (h)	0.522	[0.475-0.569]	4.6	—
Effect of food on Dur	276%	[76%-477%]	37	—
Effect of solution formulation on Dur	-69.3%	[-85.6% - -52.9%]	12	—
Effect of food on Ka	-85.7%	[-100% - -71.2%]	8.6	—
Weight on CL/F (allometry)	0.75	FIXED	—	—
Weight on Vc/F (allometry)	1	FIXED	—	—
Age <3 months on CL/F	-17.1%	[-54.8%-20.6%]	113	—
Age 3 months to <6 years on CL/F	38.2%	[15.5%-60.9%]	30	—
Albumin CL/F (power)	1.1	[0.746-1.45]	16	—
Albumin on Vc/F (power)	0.979	[0.585-1.37]	21	—
Total bilirubin on CL/F (power)	-0.268	[-0.389 - -0.146]	23	—
Healthy Volunteer on CL/F	30.1%	[9.23%-51%]	35	—
BSV on Ka (%CV)	169	[113-234]	10	30
BSV on Dur (%CV)	41.5	[18.5-57.4]	20	58
BSV on CL/F (%CV)	50.9	[43.8-57.4]	6.1	3.4
BSV on Vc/F (%CV)	45.2	[38.1-51.6]	6.9	17
Proportional error	51.5	[48.6-54.2]	2.8	5.3

Source: laro-prm-table-final-20190211-boot.R
CL/F=apparent clearance; Dur=duration of zero-order absorption; ka=first-order absorption rate constant; PK=pharmacokinetic; Q/F=apparent inter-compartmental clearance; RSE=relative standard error of the estimate; Vc/F=apparent central volume of distribution; Vp/F=apparent peripheral volume of distribution.



Source: laro-pk-gof-final-20190207.R
Cond=conditional; Ind=individual; ln=natural logarithm; PK=pharmacokinetic; Pop=population.
Note: The circles represent individual data points, the grey lines represent loess smooth curves, and the dashed and solid lines represent either the line of unity (y=x) or the x-axis (y=0).

Figure 9: Selected Goodness-of-Fit Plots for Final Population PK Model for Larotrectinib



Source: laro-pk-vpc-final-20190128.R
ln=natural logarithm; PK=pharmacokinetic; VPC=visual predictive check.
Note: The blue x-marks represent prediction-corrected observed data, the red solid line represents the median of the prediction-corrected observed data, and the red dashed lines represent the 5th and 95th quartiles of the prediction-corrected observed data. The black solid line represents the median of the prediction-corrected simulation data, the black dashed lines represent the 5th and 95th quartiles of the prediction-corrected simulation data, the blue shaded areas represent the 90% prediction interval for the 5th and 95th quartiles of the predicted data, the red shaded areas represent the 90% prediction interval for the median of the predicted data, and the yellow vertical ticks on x-axis represent the edges of the bins used to group the data for calculation of the quartiles.

Figure 10: Prediction-Corrected VPC for the Final Population PK Model for Larotrectinib stratified by study

Absorption

The absolute bioavailability was estimated to be 34% (range: 32% to 37%) in the mass balance study following an oral dose of 100 mg larotrectinib capsule formulation in the fasted state and intravenous administration of 7.6 µg (1 µCi) ^{14}C-larotrectinib.

In cancer patients given larotrectinib capsules (LOXO-TRK-14001), peak plasma levels (C_{max}) of larotrectinib were achieved at approximately 1 hour after dosing. Half-life (t½) is approximately 3 hours and steady state is reached within 8 days with a systemic accumulation of 1.6 fold. At the recommended dose of 100 mg taken twice daily, steady state arithmetic mean (± standard deviation) C_{max} and daily AUC in adults were 914 ± 445 ng/mL and 5410 ± 3813 ng*h/mL, respectively (section 5.2 of the SmPC).

- *Bioequivalence*

No bioequivalence studies were performed as the final formulation of the capsule was used in all clinical studies and there only was a minor modification of the oral solution.

- *Relative bioavailability capsule formulation vs oral solution*

The plasma AUC was similar following dosing with solution and capsule formulations, but the C_{max} was 36% higher with the solution and the time taken to reach the maximum concentration (T_{max}) was approximately 20 minutes earlier for the solution compared to the capsule, see Figure 10 and Table 20. Both formulations have been used in efficacy studies in patients with cancer.

- *Food interaction*

Administration of a high-fat and high-calorie meal delayed the absorption of larotrectinib relative to administration under overnight fasting conditions. The total plasma exposure (AUC_{0-t} and $AUC_{0-\infty}$) was comparable following fasted and fed conditions. The median t_{max} was delayed with approximately 2 hours and the C_{max} was 35% lower under fed conditions compared to fasting conditions, see Figure 10 and Table 20. The lower C_{max} under fed conditions is not considered clinically relevant and larotrectinib may be given without regard to food intake. The excretion of unchanged larotrectinib in urine following administration of a single 100 mg capsule was similar under fed and fasting conditions.

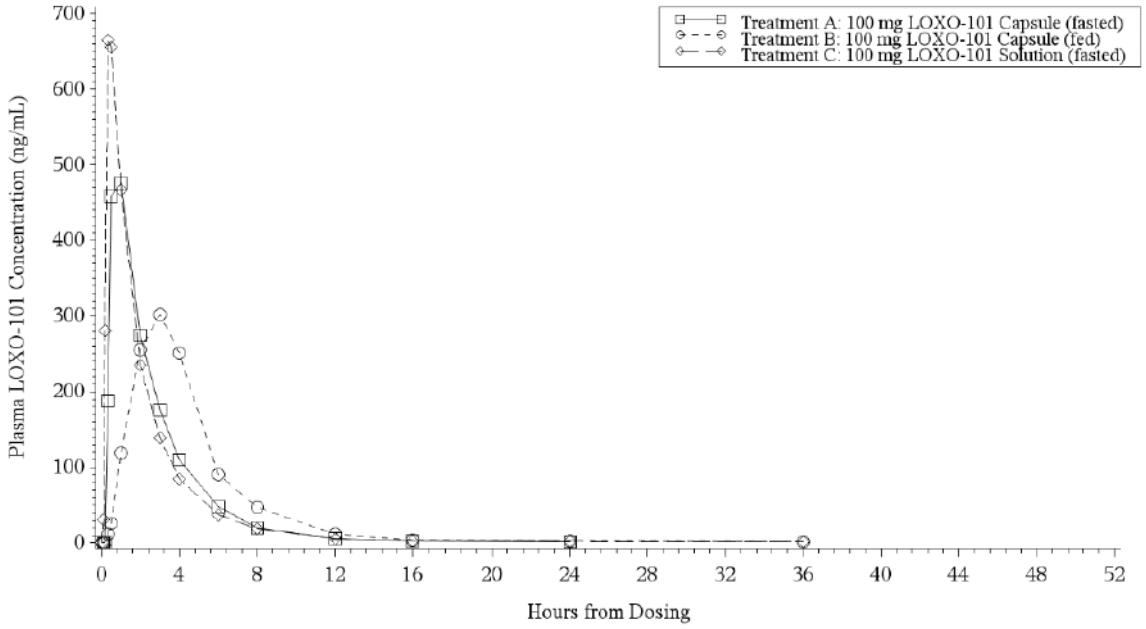


Figure 11: Arithmetic Mean Plasma Concentration-Time Profiles of Larotrectinib Following the Administration of 100 mg Larotrectinib Capsule under Fasted conditions, 100 mg Larotrectinib Capsule under Fed Conditions, and 100 mg Larotrectinib Oral Solution under Fasted Conditions

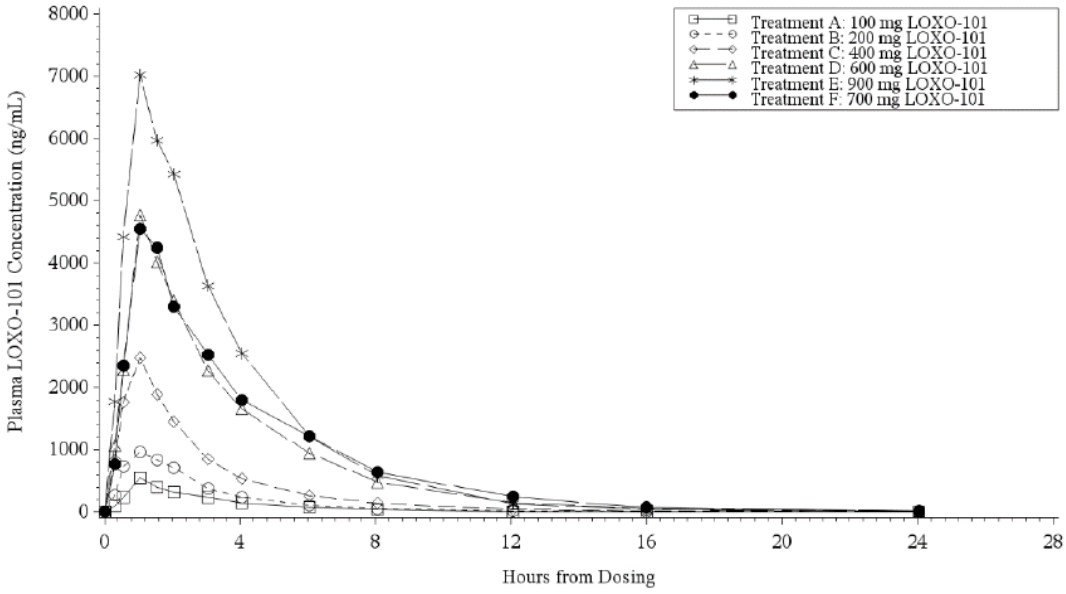


Figure 12: Arithmetic Mean Plasma Larotrectinib Concentration-Time Profiles Following Single Oral Administration of 100 to 900 mg Larotrectinib in LOXO-TRK- 16009

Distribution

The mean volume of distribution of larotrectinib in healthy adult subjects was 48 L following intravenous administration of an IV microtracer in conjunction with a 100 mg oral dose. The volume of distribution during the terminal phase following IV dosing (Vz) in plasma was 66 L.

Larotrectinib was moderately bound in human plasma over the concentration range 0.1-10 µM with an overall mean fraction unbound of 30%. The plasma protein binding was not concentration-dependent. The fraction unbound was approximately 30% also in the clinical studies LOXO-TRK-16013 (hepatic impairment) and LOXO-TRK-17014 (renal impairment) and not affected by decreased organ function. The blood to plasma concentration ratio was approximately 0.9.

Metabolism

Larotrectinib was metabolised predominantly by CYP3A4/5 in vitro. Larotrectinib was extensively metabolised following an oral dose of ^{14}C-larotrectinib with 19 identified metabolites and 12 additional quantified metabolites in plasma, urine and faeces samples from the mass balance study. Larotrectinib and M14 were the major radiolabeled components in plasma from all subjects, when analysed individually. Mean plasma exposures (AUC0-∞) for LOXO-101 and M14, a glucuronide conjugate, were 1100 ng*eq· h/g (18.6% of total plasma radioactivity exposure) and 1510 ng*eq·h/g (25.7% of total plasma radioactivity exposure) across all subjects. All remaining plasma metabolites were present at trace to minor levels. M14 was not believed to contribute to the efficacy or safety of larotrectinib. No other plasma metabolite accounted for more than 4% of total plasma radioactivity. M14 was the most abundant urinary metabolite and accounted for a mean of 9.4% of dose in urine but was not detected in faeces. The radioactivity in faeces consisted of many metabolites in smaller amounts.

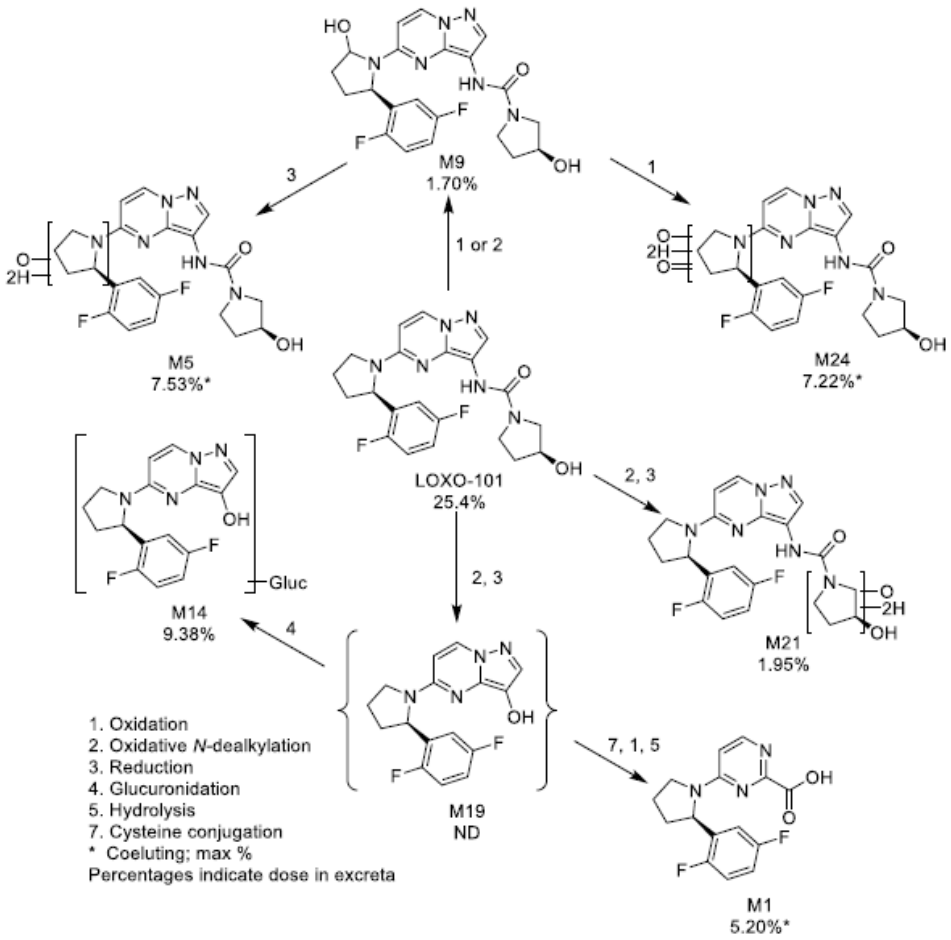


Figure 13: Major Biotransformation Pathways of Larotrectinib after a Single 100 mg (~100 µCi) Oral Dose of [^{14}C] Larotrectinib to Healthy Male Subjects: Part 1 of LOXO-TRK-16011

Elimination

The half-life of larotrectinib in plasma of cancer patients given 100 mg twice daily of larotrectinib was approximately 3 hours. The main elimination route was hepatic metabolism via CYP3A4 enzyme and excretion of metabolites in both urine and faeces.

- *Mass balance*

The mass balance study LOXO-TRK-16011 was a two-part study including both oral and IV administration of [^{14}C]-larotrectinib with a higher oral radiolabelled dose (100 mg /100 µCi) and a microtracer design of the IV dose (7.58 µg /1 µCi). The results of the mass balance study is summarised in Table 26 and Figure 14. Mean clearance (CL) of larotrectinib was approximately 34 L/h following intravenous administration of an IV microtracer in conjunction with a 100 mg oral dose of larotrectinib.

Table 26: Summary of Absorption, Metabolism, and Excretion Parameters of Larotrectinib in LOXO-TRK-16011.

Parameter	Part 1 100 mg, (100 µCi) Oral Dose	Part 2 100 mg (nonlabeled) Oral Dose	Part 2 7.58 µg, (1 µCi) IV Dose
Larotrectinib Plasma PK Parameters, Geometric Mean (Geometric %CV)			
AUC_{0-t} (h*ng/mL)	954 (37.0)	1010 (44.0)	0.216 (40.8)
AUC_{0-inf} (h*ng/mL)	965 (36.6)	1020 (43.8)	0.217 (40.6)
C_{max} (ng/mL) [a]	542 (35.8)	418 (39.8)	0.301 (59.0)
T_{max} (h), median (range)	0.500 (0.500, 0.533)	0.708 (0.500, 1.03)	0.0333 (0.0333, 0.167)
$t_{1/2}$ (h), arithmetic mean (SD)	2.93 (2.70)	2.91 (1.52)	1.38 (0.105)
CL/F (L/h)	104 (36.7)	98.0 (43.8)	NA
CL (L/h)	NA	NA	33.6 (42.0)
Vz/F (L)	353 (109.5)	374 (47.5)	NA
Vz (L)	NA	NA	66.5 (39.8)
Absolute Oral Bioavailability	NA	0.343 (6.7)	NA
Larotrectinib and Metabolites in Plasma (Fraction of Radioactivity in a Pooled Plasma Sample Representing $AUC_{0.5-24\ hours}$)[a]			
Larotrectinib (%)	22.3	NA	NA
M14 (%)	29.7	NA	NA
Others (%)	< 10	NA	NA
Renal Excretion (Larotrectinib)			
F_e (%)	19.9	8.33 (17.3)	29.1 (11.4)
CLr (L/h)	-	8.16 (35.4)	9.78 (39.5)
Excretion Mass Balance (Larotrectinib + Metabolites), Mean (%CV)			
Urine (%)	39.2	NA	53.2 (6.4)
Feces (%)	57.8	NA	34.7 (26.1)
Total (%)	97.1	NA	88.7 (9.1)

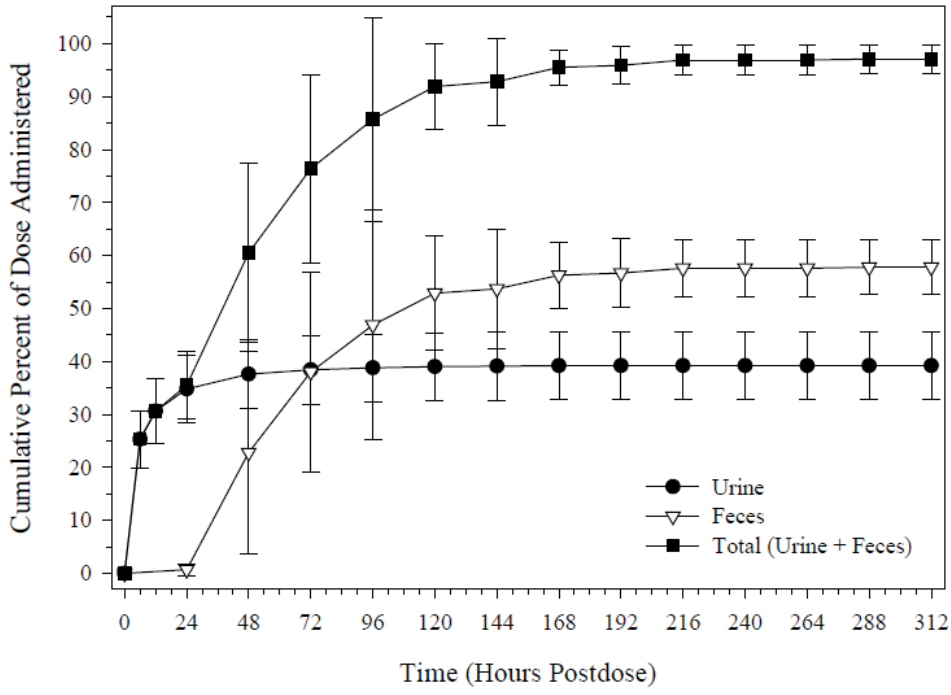


Figure 14: Mean (±SD) cumulative percent of radioactive dose recovered in urine and faeces at specified intervals after a single 100-mg (~100-µCi) oral dose of [^{14}C]-larotrectinib to healthy male subjects – Part 1

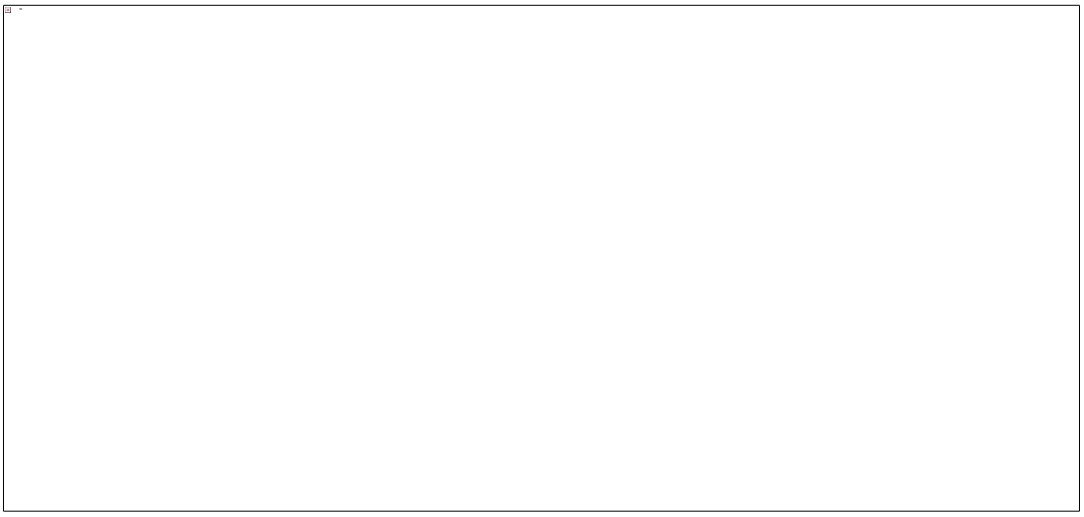


Figure 15: Mean % of dose identified in urine and faeces following oral administration of ^{14}C-larotrectinib.

When an IV microtracer dose was given in conjunction with a 100 mg oral dose of larotrectinib, 35% of the administered radioactivity was recovered in faeces and 53% was recovered in urine. Following the IV dose, 29% of [^{14}C]-larotrectinib was excreted as unchanged drug in urine.

Dose proportionality and time dependencies

A statistical assessment of dose linearity was performed on single-dose data from study LOXO-TRK-16009, see Figure 11 and Table 20. A slightly more than dose proportional increase in AUC with dose was observed, with a slope estimate of 1.3 and a 95% CI not including 1 when all data in the dose range 100-900 mg was used. When only PK data from dose levels 100 to 400 mg were considered, dose proportionality was shown. Dose proportionality has not been investigated for doses lower than 100 mg. No formal dose-linearity assessment was performed on the PK data from multiple dosing.

In study LOXO-TRK-14001, BID dosing of larotrectinib was tested in ascending dose levels. PK sampling was performed on day 1 and day 8. For the clinical dose level 100 mg x 2, where most data were available, a somewhat lower average CL/F and longer half-life of larotrectinib was observed on day 8. This is in line with data from study LOXO-TRK-1602, where steady state data indicate slightly lower Cl/F and longer half-life at steady state. The estimated mean accumulation ratio was 1.23 and 1.6 in the two studies.

Pharmacokinetics in target population

Average (SD) steady state AUC_{0-24} was 5410 (3813) ngxh/ml and average C_{max} was 914 (445) ng/ml at the clinical dose 100 mg BID.

Based on the population pharmacokinetic analysis, the inter-patient variability in CL/F was 73%. Intra-patient (inter-occasion) variability was not assessed.

Special populations

- *Renal impairment*

A dedicated pharmacokinetic study with reduced design, in subjects with end stage renal disease and matched-control adult subjects with normal renal function was included in the application. Geometric least squares mean plasma larotrectinib AUC0-t, AUC0-inf, and Cmax were approximately 1.40-fold, 1.46-fold, and 1.25-fold greater, respectively, in subjects with end stage renal disease compared to healthy matched subjects (Table 27).

Table 27: Summary of Statistical Comparisons of Plasma Larotrectinib Pharmacokinetic Parameters Following Administration of a Single Oral Dose of 100 mg Larotrectinib to Subjects with End Stage Renal Disease versus Healthy Matched Control Subjects under Fasted Conditions in LOXO-TRK-17014

	ESRD		Healthy			
Parameter	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	90% Confidence Interval
AUC_{0-t} (ng*h/mL)	1680	8	1204	8	139.56	85.09 - 228.88
AUC_{0-inf} (ng*h/mL)	1701	8	1167	7	145.77	86.59 - 245.38
C_{max} (ng/mL)	534.0	8	425.7	8	125.43	76.28 - 206.23

AUC_{0-t} = AUC to last measured concentration; AUC_{0-inf} = AUC extrapolated to infinity;.
Geometric least-squares means (LSMs) calculated by exponentiating the LSMs from the ANCOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)

- *Hepatic impairment*

A pharmacokinetic study was conducted in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, and in healthy adult control subjects with normal hepatic function matched for age, body mass index and sex. All subjects received a single 100 mg dose of larotrectinib. An increase in larotrectinib AUC_{0-inf} was observed in subjects with mild, moderate and severe hepatic impairment of 1.3, 2 and 3.2-fold respectively versus those with normal hepatic function. C_{max} was observed to increase slightly by 1.1, 1.1 and 1.5-fold respectively. (Figure 15).

Figure 16: Arithmetic Mean Plasma Concentration Profiles of Larotrectinib in Subjects with Mild, Moderate or Severe Hepatic Impairment, and Healthy Matched Controls Given a 100 mg Oral Dose of Larotrectinib under Fasted Conditions in LOXO-TRK-16013

- *Children*

Interim results (cut-off date July 30th, 2018) from the ongoing phase 1/2 Study of larotrectinib in Paediatric Patients with Advanced Solid or Primary Central Nervous System Tumours have been presented. Pharmacokinetic data were available from 58 paediatric patients. Initially paediatric subjects received doses ranging from 9.6 mg/m^2 BID to 120 mg/m^2 BID. The dose of 100 mg/m^2 BID (up to a maximum dose of 100 mg BID) in children was chosen to match the adult exposures when administered 100 mg BID.

Figure 16 and Figure 17 show larotrectinib exposure (calculated using non-compartmental analysis) versus age and BSA was provided for the paediatric patients.

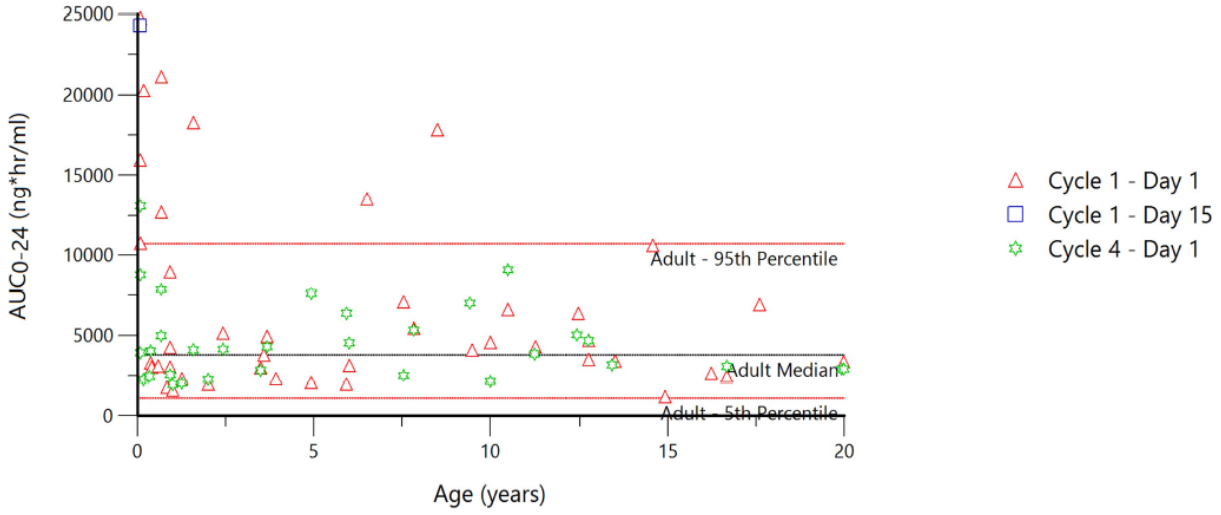


Figure 17: Paediatric exposure (AUC0-24) versus Age in patients receiving 100 mg/m2 BID

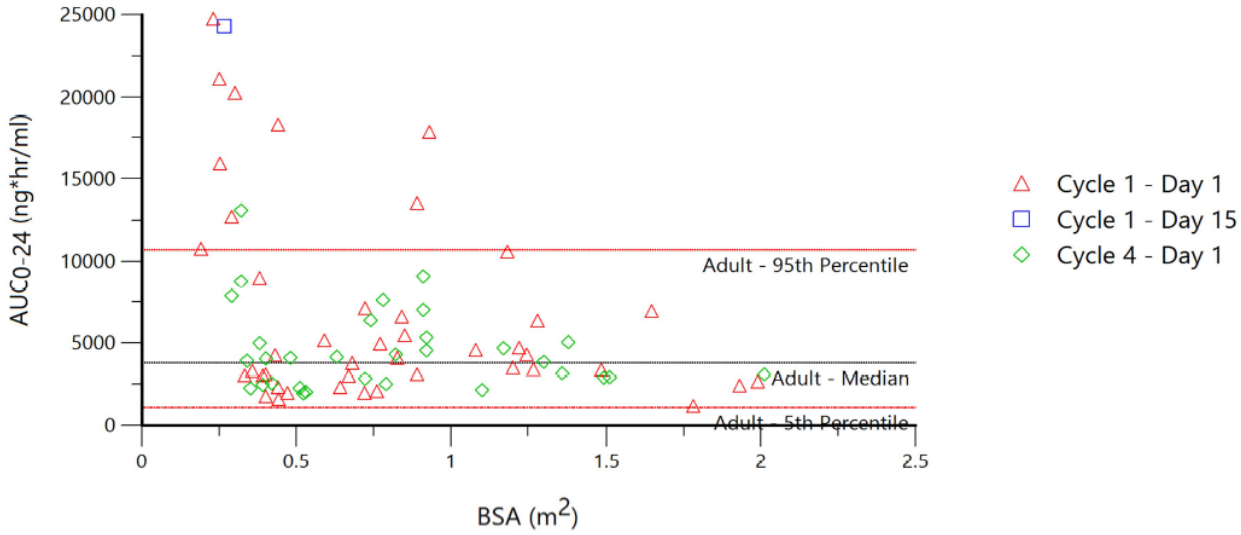
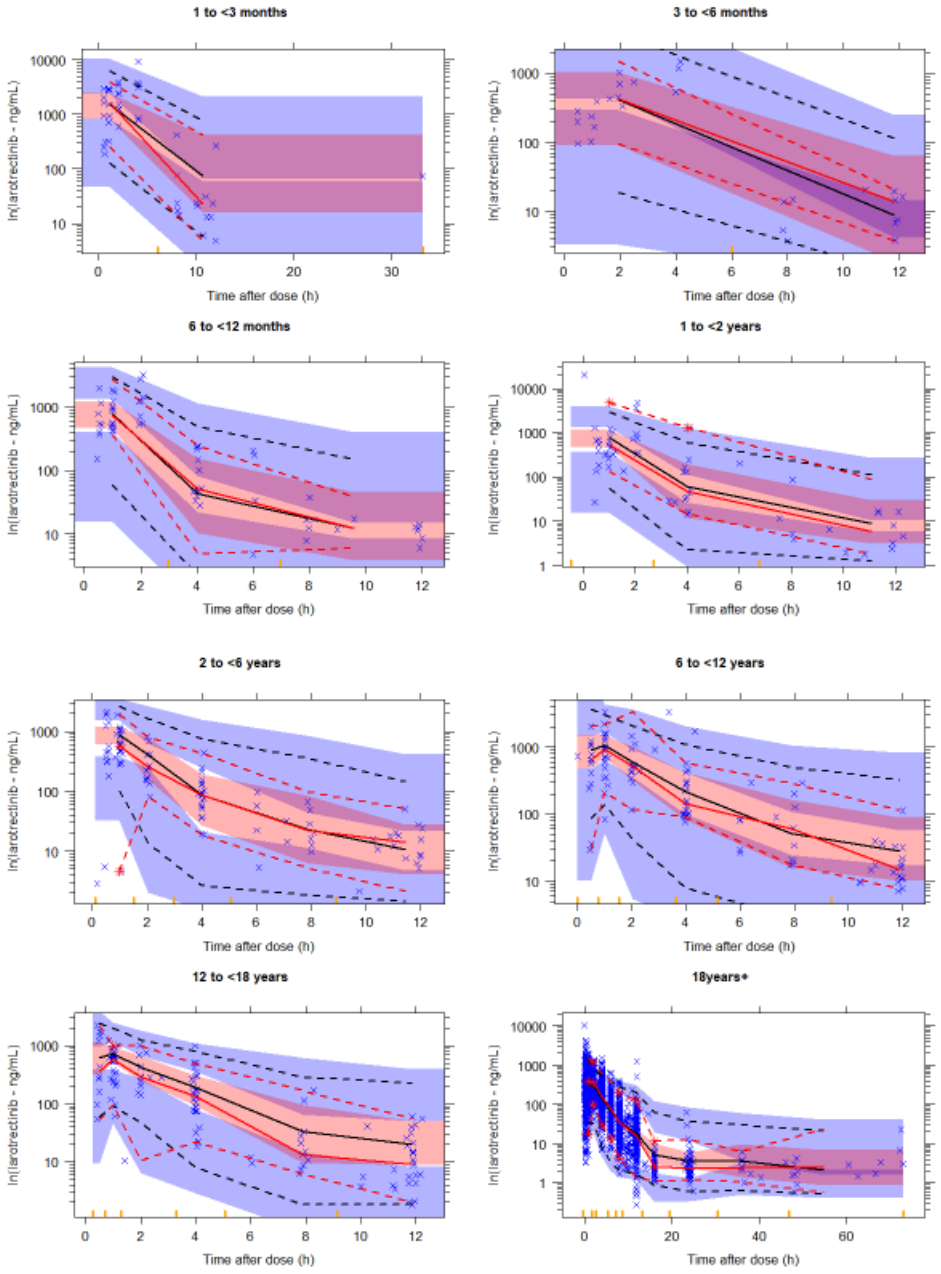


Figure 18: Paediatric exposure (AUC0-24) versus Body Surface Area in patients receiving 100 mg/m2 BID with maximum of 100 mg BID in study LOXO-TRK-15003. Linear y-axis. N=75 observations. Cycle 1 day 1, n=43; Cycle 1 day 15, n=1; Cycle 4 Day 1, n=31

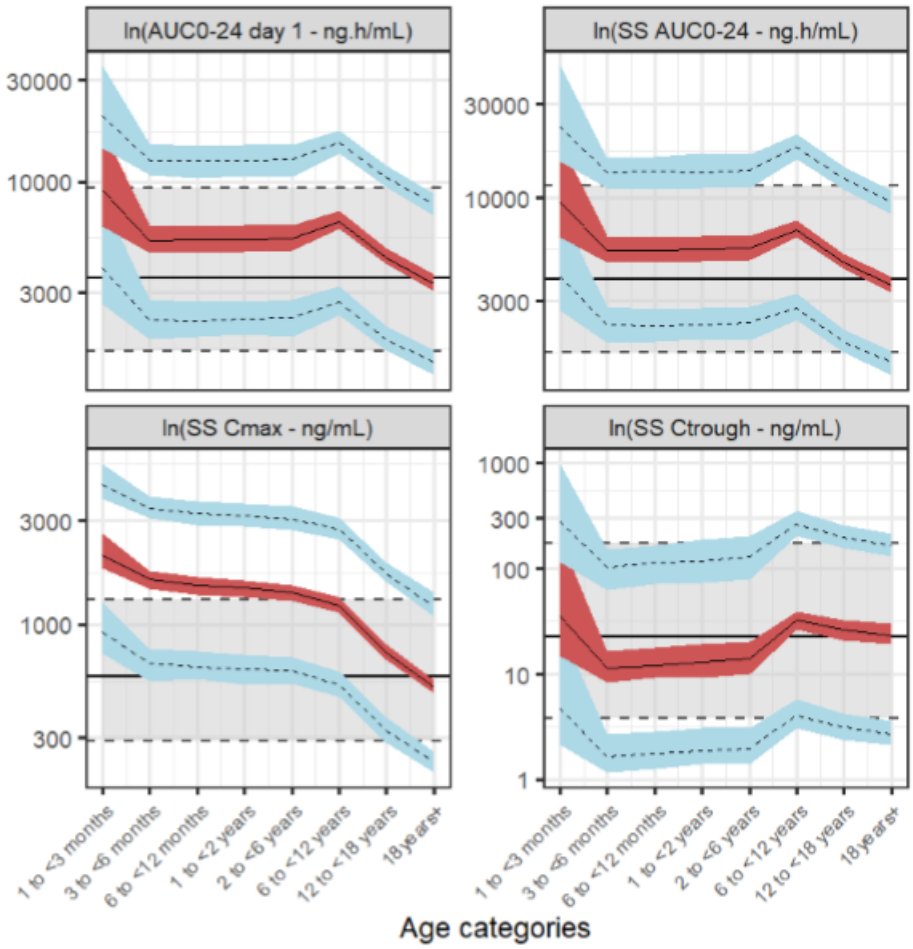
The final population PK model prediction corrected visual predictive check plots (pcVPCs,

Figure **18**) and plots of simulated exposures (Figure 19 and Figure 20) for paediatric patients <18 years of age are presented below.



Source: laro-pk-vpc-final-20190128.R
ln=natural logarithm; PK=pharmacokinetic; VPC=visual predictive check.
Note: The blue x-marks represent prediction-corrected observed data, the red solid line represents the median of the prediction-corrected observed data, and the red dashed lines represent the 5th and 95th quartiles of the prediction-corrected observed data. The black solid line represents the median of the prediction-corrected simulation data, the black dashed lines represent the 5th and 95th quartiles of the prediction-corrected simulation data, the blue shaded areas represent the 90% prediction interval for the 5th and 95th quartiles of the predicted data, the red shaded areas represent the 90% prediction interval for the median of the predicted data, and the yellow vertical ticks on x-axis represent the edges of the bins used to group the data for calculation of the quartiles.

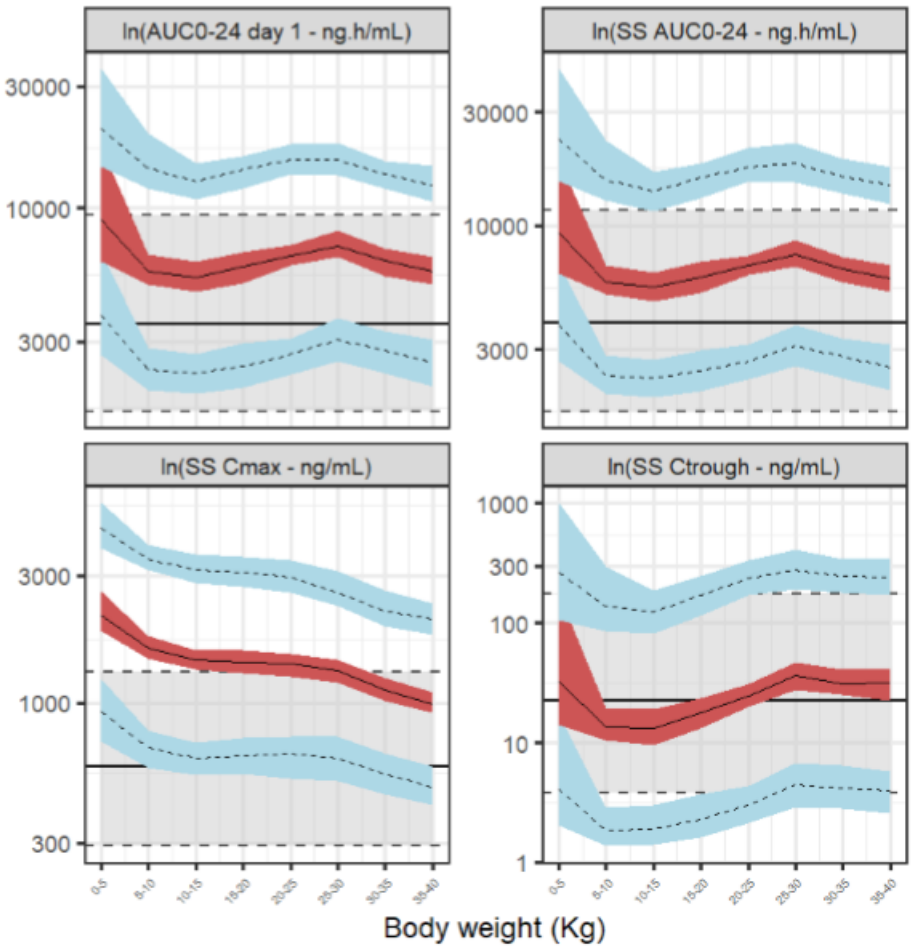
Figure 19: Prediction-Corrected VPC for the Final Population PK Model for Larotrectinib Stratified by Age Group



AUC_{0-24}=area under the plasma concentration-time curve from 0 to 24 hours; C_{max}=peak concentration; Ctrough=trough concentration; ln=natural logarithm; SS=steady-state.

Note: Blue shaded regions represent the 95% prediction interval for the 5th and 95th quartiles of the simulated data. The black dashed line within the blue shaded region represents the median of the 5th and 95th quartiles of the simulated data. Red shaded region represents the 95% prediction interval for the 50th quartile (median) of the simulated data. The solid black line within the red shaded region represents the median of the 50th quartile of the simulated data. Grey shaded region represents the 5th to 95th quartiles of the adult exposure for the patients in the population PK dataset. The horizontal dashed lines represent the 5th and 95th quartiles and the horizontal solid line represents the 50th quartile (median) of the adult exposure for the patients in the population PK dataset.

Figure 20: Simulated Larotrectinib Exposure Grouped by Age (logarithmic scale)



AUC_{0-24}=area under the plasma concentration-time curve from 0 to 24 hours; C_{max}=peak concentration; Ctrough=trough concentration; ln=natural logarithm; SS=steady-state.

Note: Blue shaded regions represent the 95% prediction interval for the 5th and 95th quartiles of the simulated data. The black dashed line within the blue shaded region represents the median of the 5th and 95th quartiles of the simulated data. Red shaded region represents the 95% prediction interval for the 50th quartile (median) of the simulated data. The solid black line within the red shaded region represents the median of the 50th quartile of the simulated data. Grey shaded region represents the 5th to 95th quartiles of the adult exposure for the patients in the population PK dataset. The horizontal dashed lines represent the 5th and 95th quartiles and the horizontal solid line represents the 50th quartile (median) of the adult exposure for the patients in the population PK dataset.

Figure 21: Simulated Larotrectinib Exposure Grouped by Body Weight for Paediatric Patients <40kg of Body Weight (logarithmic scale)

Table 28: GMRs of Larotrectinib Exposures in Paediatric Patients Receiving the BSA-based Dosing Regimen vs Adults Reference Exposure – Grouped by Age

Parameter	Age Category Contrast	N	GMR	90% CI
AUCss	<3 months (test) vs adults (ref)	4	3.18	1.96-5.16
	3-6 months (test) vs adults (ref)	2	1.05	0.53-2.08
	6 months to 1 year (test) vs adults (ref)	7	1.18	0.82-1.71
	1-2 years (test) vs adults (ref)	7	1.27	0.88-1.84
	2-6 years (test) vs adults (ref)	13	1.13	0.87-1.49
	6-12 years (test) vs adults (ref)	12	1.49	1.12-1.99
	12-18 years (test) vs adults (ref)	15	0.92	0.71-1.19
C_{max}	<3 months (test) vs adults (ref)	4	3.33	2.27-4.88
	3-6 months (test) vs adults (ref)	2	2.1	1.22-3.59
	6 months to 1 year (test) vs adults (ref)	7	1.79	1.34-2.41
	1-2 years (test) vs adults (ref)	7	2.2	1.63-2.98
	2-6 years (test) vs adults (ref)	13	2	1.61-2.48
	6-12 years (test) vs adults (ref)	12	1.76	1.4-2.21
	12-18 years (test) vs adults (ref)	15	1.09	0.88-1.36
C_{trough}	<3 months (test) vs adults (ref)	4	2.95	1.08-8.07
	3-6 months (test) vs adults (ref)	2	0.29	0.07-1.18
	6 months to 1 year (test) vs adults (ref)	7	0.42	0.19-0.89
	1-2 years (test) vs adults (ref)	7	0.57	0.27-1.23
	2-6 years (test) vs adults (ref)	13	0.41	0.23-0.72
	6-12 years (test) vs adults (ref)	12	1	0.55-1.8
	12-18 years (test) vs adults (ref)	15	0.6	0.35-1.02
AUC day 1	<3 months (test) vs adults (ref)	4	3.3	2.13-5.13
	3-6 months (test) vs adults (ref)	2	1.12	0.6-2.09
	6 months to 1 year (test) vs adults (ref)	7	1.26	0.9-1.77
	1-2 years (test) vs adults (ref)	7	1.35	0.97-1.89
	2-6 years (test) vs adults (ref)	13	1.21	0.95-1.55
	6-12 years (test) vs adults (ref)	12	1.56	1.2-2.03
	12-18 years (test) vs adults (ref)	15	0.96	0.76-1.22

Source: Addendum 2 of Report R-12852: "Integrated Exploratory Population Pharmacokinetic Analysis of Larotrectinib of Studies 20291 (LOXO-TRK-16007), 20295 (LOXO-TRK-16012), 20288 (LOXO-TRK-14001), 20289 (LOXO-TRK-15002), and 20290 (LOXO-TRK-15003)"
AUC day 1=area under the plasma concentration-time curve at day 1; AUCss=area under the plasma concentration-time curve at steady-state; CI=confidence interval; C_{max}=maximum concentration at steady-state; C_{trough}=trough concentration at steady-state; GMR=geometric mean ratio; ref=reference
Note: all exposure values were determined from simulated larotrectinib concentration-time data at steady-state using subjects included in the population PK dataset and the associated individual subject posthoc PK parameters with the proposed therapeutic dose in adults of 100 mg larotrectinib BID, and in pediatrics of 100 mg/m^2 larotrectinib BID up to a maximum dose of 100 mg larotrectinib BID. GMR and 90% CI were calculated for each comparison of test divided by reference.

- *Gender, Race, Weight and Elderly*

In the popPK analysis, 131 male and 109 female subjects were included, 173 subjects were classified as Caucasian, 27 patients as Black or African American, 9 patients as Asian, 1 patient as Alaska or American Indian, 1 patient as Hawaiian or Pacific Islander and 29 patients as Other. The weight range was 3.1 to 179.4 kg. Gender and race were not formally tested as covariates in the model. A graphical screening was performed, and there was no obvious correlation between gender and race and the PK parameters. Weight was found to have a significant impact on larotrectinib CL and V. The PK dataset of larotrectinib included only two patients above the age of 65.

Table 29: Clinical studies in elderly populations

	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	2 / 169	No patients 75-84 years of age were included in PK studies	No patients 85 years or older were included in PK studies

- *Healthy subjects*

Mean half-life in healthy subjects ranged from 1.876 to 6.347 hours. In patients, with a QD administration, mean half-life ranged from 2.99 to 4.7 h whereas in patients with a BID administration mean half-life ranged from 1.56 to 2.99h. In the population pharmacokinetic analysis 34 subjects out of 240 were healthy subjects. The CL/F was estimated to be 30% higher for healthy subjects.

Pharmacokinetic interaction studies

- *Larotrectinib as victim for drug-drug interactions*

Larotrectinib was shown to be a substrate of CYP3A4, P-gp and BCRP in vitro. Clinical data in healthy adult subjects (study LOXO-TRK-16010) indicated that co-administration of a single 100 mg larotrectinib dose with itraconazole (a strong CYP3A inhibitor and P gp and BCRP inhibitor) 200 mg once daily for 7 days increased larotrectinib C_{max} and AUC by 2.8 fold and 4.3 fold, respectively. In addition, co-administration of a single 100 mg larotrectinib dose with a single dose of 600 mg rifampin (a P-gp and BCRP inhibitor) resulted in an increase of larotrectinib C_{max} and AUC by 1.8 fold and 1.7 fold, respectively.

A study in healthy adult subjects indicated that co-administration of a single 100 mg larotrectinib dose with rifampin (a strong CYP3A and P-gp inducer) 600 mg twice daily for 11 days decreased larotrectinib C_{max} and AUC by 71% and 81%, respectively.

A PBPK model has been submitted in the second round of assessment aiming at predicting the effect of a moderate inducer, efavirenz. The model is however not sufficiently qualified to be used for quantitative predictions.

An in vitro study investigating the substrate properties of larotrectinib towards the uptake transporters OATP1B1 and OATP1B3 has been requested during assessment and the submitted results show that larotrectinib is no substrate of OATP1B1 or OATP1B3. The effect of the single dose rifampicin on larotrectinib exposure is therefore believed to be due to inhibition of P-gp and BCRP with no involvement of OATP1B1 or OATP1B3.

No DDI study with drugs affecting gastric pH has been performed. Larotrectinib has pH dependent solubility. In vitro studies show that in liquid volumes relevant to the gastrointestinal (GI) tract larotrectinib is fully soluble over entire pH range of the GI tract.

- *Larotrectinib as perpetrator for drug-drug interactions*

For both CYP3A4 and CYP2B6, significant induction was seen for larotrectinib in vitro with observed concentration-dependent increases in CYP3A4 mRNA and CYP2B6 mRNA levels. No induction of CYP1A2 was seen. In vitro induction data for CYP2C8, CYP2C9 and CYP2C19 showed no or minor induction but the results was not considered conclusive due to a very low response to the positive control rifampicin. Based on the strong induction signal observed for CYP3A4, larotrectinib is still considered a potential PXR inducer in vivo. New in vitro data for larotrectinib as an inducer of CYP2C enzymes will be submitted.

In vitro larotrectinib caused time dependent inhibition of CYP3A4. In vitro studies indicate that larotrectinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations and is unlikely to affect clearance of substrates of these CYPs. No inhibition of OAT1, OCT1, OATP1B3, BCRP, OCT2 and BSEP was observed at 30 uM larotrectinib. For OAT3, MATE1 and MATE2-K some inhibition was observed but at concentrations similar or higher than the cut-off for clinical relevance. Inhibition of OATP1B1 was observed with an IC50 of 48 uM. In vitro results of P-gp inhibition have shown that larotrectinib is not a P-gp inhibitor.

In a clinical study (LOXO-TRK-16012) with midazolam (a sensitive CYP3A4 substrate), 10 days of dosing larotrectinib 100 mg twice daily to healthy volunteers led to a 1.7–fold increase in midazolam C_{max} and AUC_{inf}, indicating that the net effect (inhibition + possible induction) of larotrectinib on CYP3A4 is inhibition, and that larotrectinib at the 100 mg twice daily dosing is a weak CYP3A4 inhibitor (see section 4.5 of the SmPC).

- *Systemic hormonal contraceptives*

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

2.4.3. Pharmacodynamics

Mechanism of action

No dedicated mechanism of action studies were submitted by the applicant.

Vitrakvi (larotrectinib) is an orally bioavailable targeted agent directed against TRK-fusion proteins.

Tropomyosin receptor kinases (TRKs) are a family of tyrosine kinases that bind neurotrophins, a family of growth factors important to the formation and function of the nervous system. In cancer, the neurotrophic tyrosine kinase receptor (NTRK), NTRK1, NTRK2, and NTRK3 genes, which encode for the TRKA, TRKB, and TRKC proteins, respectively, are subject to gene re-arrangements that lead to aberrant TRK protein expression with ligand-independent constitutive kinase activity and subsequent constitutive downstream pathway activation, including pathways involved in cell proliferation and survival. NTRK gene fusions appear to be widely distributed across histologically diverse adult and paediatric cancers.

In normal physiology, TRK receptors are involved in the regulation of pain (TRKA), memory and weight regulation (TRKB) and proprioception (TRKC).

Primary and Secondary pharmacology

Relationship between plasma concentration and response

Interim data from three ongoing clinical studies (LOXO-TRK-14001 (adult patients, n=56), LOXO-TRK-15002 (patients age >12 years, n=40) and LOXO-TRK-15003 (paediatric patients, n=23)) were included in the exposure-response analysis (Table 22). The overall best response (complete or partial response) was analysed using a generalized linear model. The log-odds ratio (i.e. the logit of the probability) described the probability of a response on the predictors of interest. Several predictors were evaluated, and among these, exposure measures were included (calculated using non-compartmental methods). The first analysis included all patients, regardless of fusion protein status, and the predictors found were NTRK fusion (strongest predictor), absolute neutrophil count, and prior radiation treatment (yes/no). None of the larotrectinib exposure measures tested (e.g., AUC, Cavg, or Cmax) had a statistically significant effect on the probability of a response. A subgroup analysis was also conducted in in the positive NTRK fusion patients. The predictor found in the model was absolute neutrophil count.

Relationship between larotrectinib exposure and QTcF prolongation

In a placebo controlled, single ascending dose study, 36 healthy adult subjects were administered single doses ranging from 100 mg to 900 mg larotrectinib, holter monitors were used to collect continuous 12-lead ECG data from pre-dose until 24 hours post-dose. The relationship between larotrectinib concentrations and dQTc was explored using a linear mixed-effect model. The model diagnostics indicate a delay between Cmax and the highest observed change that has not been accounted for. The slope of the regressions of ddQTcF on larotrectinib was negative, -0.0005 (90% CI: -0.0008, -0.0003) and was statistically significant with p-value of 0.0004. Larotrectinib did not prolong the QT interval to any clinically relevant extent.

The 200 mg dose corresponds to a peak exposure (C_{max}) similar to that observed with larotrectinib 100 mg BID at steady state. A shortening of QTcF was observed with larotrectinib dosing, with a maximum mean effect observed between 3 and 24 hours after C_{max}, with a geometric mean decrease in QTcF from baseline of 13.2 msec (range 10 to 15.6 msec).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Methods

The bioanalysis methods used are acceptable.

The Applicant has developed a population PK model to describe the PK data from the clinical studies. The model includes allometric scaling with fixed exponents of 0.75 for clearance parameters and an exponent of 1 for volume parameters. The difference in CL/F values for different age categories were described with an age category effect on CL/F with 3 distinct age groups (<3 months, ≥3 months to <6 years, and ≥6 years). Overall, the model appears to capture the median of the observed data reasonably well. It should however be noted that the amount of data in the youngest age groups are limited, and the estimation of the age category effects may be refined when more data emerge.

ADME

The results of in vitro permeability data are not considered conclusive and the absolute bioavailability is estimated to 34%. Based on the high solubility and that absorption data do not indicate high absorption, larotrectinib is probably a BCS class III compound.

The food interaction study showed similar AUC and somewhat lower C_{max} (34%) when larotrectinib was given with a high fat food compared with fasting conditions. The lower C_{max} is not expected to have clinical relevance, and the data supports the clinical recommendation that larotrectinib can be taken irrespective of meals (see section 4.2 of the SmPC). The formulations to be marketed have been used in the clinical studies. The solution and the capsule have the same bioavailability, and the higher Cmax seen with the solution (36%) is considered of no clinical relevance. The mean volume of distribution indicates moderate distribution into tissues from the plasma.

The elimination pathways of larotrectinib are considered sufficiently elucidated. Around 29% of the dose is excreted unchanged in urine indicating that direct renal excretion accounted for 29% of total clearance. The majority of the remaining drug is excreted in urine and faeces as metabolites, mainly produced by CYP3A4. This is supported by the relatively large effect seen in the interaction study with the strong CYP3A4 inhibitor itraconazole.

In the mass-balance study, metabolite profiling was performed following an oral dose and more than 90% of the recovered radioactivity in urine was identified. However, in faeces quantified components accounted for a mean of 31.5% of dose compared to the total radioactivity recovered in faeces, which was

55% of dose. The applicant suggests the presence of numerous trace-level metabolites that were below the limit of quantification as an explanation of the difference. This explanation is considered acceptable. In plasma, approximately 58% of the total radioactivity was identified. This is considered acceptable since the major metabolite (M14), contributing to approximately 30% of the AUC of drug related material, is structurally characterised. No other plasma metabolite accounted for more than 4% of total plasma radioactivity.

Metabolite M14 is a secondary glucuronide and not expected to contribute to the efficacy and safety of larotrectinib. Therefore, further characterisation if its pharmacokinetics is not considered necessary.

Larotrectinib is chiral and has two chiral centres. No specific studies were performed to investigate interconversion in vivo. The optical purity in the starting material however was high and no interconversion has been observed in vitro. This indicates that the probability of interconversion is low also in vivo.

Children

The Applicant is seeking approval of larotrectinib in children of all ages, with a body-size adjusted dose (100 mg/m^2) for the smallest children up to a BSA of 1 m^2, followed by the adult dose from 1 m^2. The Applicant has aimed at a dose producing similar exposure in children as in adults receiving 100 mg BID. As there is limited efficacy and safety data available in children, pharmacokinetic data is needed to bridge to the clinical experience in adults. In particular, given the preclinical toxicity findings in juvenile animals and the tendency to higher rate of adverse events in smaller children, it appears important not to expose children to higher larotrectinib concentrations than necessary for efficacy.

Exposure data was presented, derived using non-compartmental analysis of drug exposure, between age or BSA and AUC. The plot indicated a risk for overexposure of the smallest children. The population PK model describes the exposure in the paediatric population adequately. At the recommended dose, the C_{max} in paediatric patients (≥3 months to <12 years of age) was higher than in adults, but the AUC was similar to that in adults. For paediatric patients older than 12 years of age, the recommended dose is likely to give similar C_{max} and AUC as observed in adults.

The simulated plots show that children aged <3 months (n= 4 subjects) at the recommended dose of 100 mg/m^2 with a maximum of 100 mg BID are expected to have a GMR AUC,ss and C_{max} >3-fold higher than adults ≥18 years of age given the dose of 100 mg BID. A different dose is not proposed for the smallest children. As there is uncertainty in the predicted exposure in the smallest children (< 6 years of age), due to few subjects included in each age group, there is at present not a sufficient amount of data available to be able to propose an alternative dosing in children. In particular, additional data in smaller children would be needed to be able to potentially propose a lower dose/m^2 in the smallest children, and to define an age cut-off at which a lower dose would be needed.

Given the convincing efficacy results and manageable short-term side effects of larotrectinib in children of all age groups dosed with the proposed dose 100 mg/m^2, the benefit/risk of larotrectinib in children using this dose can be considered positive. In order to avoid unnecessary overexposure, and potential risks for long-term side effects, however, the Applicant has committed to collect more PK data in children, and to re-evaluate the dose in different age groups when more data is collected.

Other special populations

The applicant performed a reduced study design in subjects with renal impairment. The ESRD patients included were all on haemodialysis; therefore, the potential effect on the hepatic elimination of the drug may be underestimated. It cannot be excluded that the effect in ESRD patients without haemodialysis may be somewhat larger due to a potential effect on hepatic elimination. The possible increase is however

not deemed to be of a clinically relevant extent and the conclusion that no dose adjustment is necessary for patients with renal impairment is supported.

The Applicant has performed a full hepatic impairment study, and the overall design appears relevant. The Applicant has submitted individual Child Pugh data to verify that the subjects in the severe hepatic impairment group had abnormal levels of biomarkers indicative of metabolic impairment (albumin, bilirubin, prothrombin time). The study can thus be considered acceptable and the Child Pugh C group representative for subjects with severe hepatic impairment.

The starting dose of VITRAKVI should be reduced by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A). Despite the wide therapeutic window, a decrease in dose is reasonable to bring this population closer in drug exposure to the average study population. Given the 3.2-fold increase in exposure observed in the study, the exposure should still be somewhat higher than the average population, which is acceptable.

Based on graphical analysis, the covariates gender and race were considered to not be significant in the PopPK model. As majority of the included patients were Caucasian, a conclusion on the potential effect of race on larotrectinib PK cannot be made. Weight was included in the model with estimated exponents. There was not sufficient PK data available in elderly (only for 2 patients over 65 years) for a conclusion to be drawn and a dose adjustment in this patient population is not recommended. Healthy subjects were found to have a 30% higher CL/F compared to patients.

Interactions

Larotrectinib was shown to be a substrate of CYP3A4, P-gp and BCRP in vitro. This was confirmed in the in vivo study with itraconazole and rifampicin.

There is a clinical drug-drug interaction study available with a strong CYP3A4/Pgp inducer rifampicin, showing a substantial decrease in larotrectinib exposure (81% lower AUC). No clinical data is available on the effect of a moderate inducer, but a decrease in larotrectinib exposure is expected. PBPK modelling of the effect of a moderate inducer, efavirenz, has been submitted, suggesting a 64% decrease in larotrectinib AUC. The model is not sufficiently qualified or reported to be used for regulatory decision making, but the predicted effect size is of an expected magnitude. Co-administration of strong or moderate CYP3A4/P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, or St. John's Wort) should be avoided with larotrectinib due to a risk of decreased exposure (see section 4.4 of the SmPC). No clinical data is available on the effect of a moderate inducer, but a decrease in larotrectinib exposure is expected.

Co administration of larotrectinib with strong CYP3A inhibitors, P gp and BCRP inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole or grapefruit) may increase larotrectinib plasma concentrations. If co administration with a strong CYP3A4 inhibitor is necessary, the larotrectinib dose should be reduced by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, larotrectinib should be resumed at the dose taken prior to initiating the CYP3A4 inhibitor (see sections 4.2 and 4.5 of the SmPC).

Theoretically, the use of Pgp inhibitors may increase the concentrations of larotrectinib in the brain with a potentially increased risk of CNS-related adverse reactions. The Applicant however argues based on literature data that the clinical risk for an increased CNS activity of drugs when combined with Pgp inhibitors in general appears to be low. This is agreed. There is no clinical data to judge whether Pgp inhibitor may increase CNS exposure to larotrectinib. Of note, larotrectinib should be dose adjusted if used together with strong CYP3A4 inhibitors, which also includes most strong Pgp inhibitors, and this would decrease the risk for a clinically relevant interaction at the blood-brain barrier.

An in vitro study investigating the substrate properties of larotrectinib towards the uptake transporters OATP1B1 and OATP1B3 has been submitted and the results show that larotrectinib is no substrate of OATP1B1 or OATP1B3. The effect of the single dose rifampicin on larotrectinib exposure (1.7-fold increase in AUC of larotrectinib) is hence believed to be due to inhibition of P-gp and BCRP with no involvement of OATP1B1 or OATP1B3.

An in vivo study with midazolam was submitted and C_{max} and AUC_{0-inf} were approximately 1.7-fold higher when midazolam was administered in combination with larotrectinib than when administered alone. This indicates that larotrectinib is a weak CYP3A4 inhibitor. Caution should be exercised with concomitant use of CYP3A substrates with narrow therapeutic range (e.g. alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus) in patients taking larotrectinib. If concomitant use of these CYP3A substrates with narrow therapeutic range is required in patients taking larotrectinib, dose reductions of the CYP3A substrates may be required due to adverse reactions (see section 4.5 of the SmPC).

Larotrectinib is an inducer of both CYP3A4 and CYP2B6 in vitro. No induction was seen in the midazolam study but the results cannot at the moment be extrapolated to other PXR regulated enzymes as larotrectinib is also an in vitro inhibitor of CYP3A4. The Applicant has provided in vitro induction data for CYP2C8, CYP2C9 and CYP2C19. No or very minor induction was observed in response to increasing concentrations of larotrectinib. The response to the positive control rifampicin was however very low, questioning the ability of the experimental setup to detect clinical CYP2C inhibitors. Based on the strong induction signal observed for CYP3A4, larotrecinib is still considered a potential PXR inducer in vivo, and induction of CYP2C enzymes (as well as other PXR regulated enzymes and transporters) in vivo cannot be excluded based on the current in vitro data due to the low sensitivity of the experimental system. The applicant is recommended to submit new *in vitro* induction data for CYP2C. If the risk for CYP2C induction cannot be excluded based on the new in vitro data, an in vivo study with a sensitive CYP2C substrate may be needed to shed light on the risk for clinical PXR induction. Awaiting these data, a warning is included in the section 4.5 of the SmPC. Co administration of larotrectinib with CYP2C8, CYP2C9 or CYP2C19 substrates (e.g. repaglinide, warfarin, tolbutamide or omeprazole) may decrease their exposure.

No in vivo study with a CYP2B6 substrate has been performed. An in vivo study is not considered an absolute requirement because there are few clinically relevant substrates of CYP2B6. The in vitro finding is however described in the SmPC. Co administration of larotrectinib with CYP2B6 substrates (e.g. bupropion, efavirenz) may decrease their exposure.

There is no clinical data addressing the effect of larotrectinib on systemic contraceptive steroids. The risk for loss of efficacy of hormonal contraceptives due to induction appears low, given the net inhibitory effect of larotrectinib on CYP3A4. However, given the in vitro inducing effects on CYP3A4 as a model for PXR induction and on CYP2B6 as a model for CAR induction, the risk for an inducing effect on e g UGT metabolism cannot be excluded. In addition, the Guideline on the Investigation of Drug Interaction recommends an in vivo DDI study with hormonal contraceptives for all human teratogens, to account also for potential mechanisms of induction that are presently unknown. The lack of knowledge is communicated in the SmPC together with a recommendation to women using systemic contraceptive steroids to add a barrier method**.**

In vitro studies evaluating the interaction potential of larotrectinib on transporters showed a signal on OATP1B1 inhibition. No clinical studies have been performed to investigate interactions with OATP1B1 substrates. Therefore, it cannot be excluded whether co administration of larotrectinib with OATP1B1 substrates (e.g. valsartan, statins) may increase their exposure (see section 4.5 of the SmPC)**.**

Larotrectinib has pH dependent solubility however it is unlikely to be affected by pH modifying agents.

Pharmacokinetic/pharmacodynamic relationship

The applicant developed an exposure-response model with the objective to identify primary predictors of response. Drug exposure parameters were calculated using non-compartmental methods which are not optimal due to sparse sampling. In addition, possible issues with the model development procedure exist, but will not be pursued further due the weak clinical relevance. During analysis of the full data set (including patients with and without NTRK fusion), the strongest predictor of response was found to be the presence of NTRK fusion. None of the larotrectinib exposure measures tested (e.g., AUC, Cavg, or Cmax) were found to have a statistically significant effect on the probability of a response. Because the dose range investigated was narrow, a definitive conclusion on the relationship between exposure and efficacy cannot be made. During model based analysis of the subgroup of patients with NTRK fusion, it was found that the patients with a lower average absolute neutrophil count had a higher response rate. A discussion on the clinical relevance of this finding in the target population was not provided. An interim exposure-safety analysis was performed using exposure metrics from the non-compartmental analysis, which is a weakness. A relationship was found between larotrectinib exposure and the risk for anaemia.

In a single ascending dose study (100-900 mg) the cardiac effect and pharmacokinetics of larotrectinib in healthy adult subjects were evaluated. A QTcF shortening was observed and the clinical relevance of this finding has not been established.

2.4.5. Conclusions on clinical pharmacology

Due to the uncertainty in exposure estimates for the youngest children, the applicant has agreed to provide and updated model including available data up to cut-off date June 2019. In addition, the Applicant has committed to continue collecting more paediatric PK data. If deemed warranted, the paediatric dose may be refined when enough PK-data is available to support a new (lower) dose.

Furthermore, due to the limited efficacy data base, comprehensive data is required post-authorisation with regard to histology-independent efficacy. Among the anatomy-based tumour types studied in a clinical trial setting there are tumour types with single patients that did not achieve objective response and it is not known if tissue-specific bypass mechanisms such as was seen for BRAF inhibitors could exist also for NTRK fusions. A conditional marketing authorisation is therefore considered.

The CHMP considers the following measures necessary to address the issues related to pharmacology in the context of a conditional MA:

- In order to further confirm the appropriate dose recommended in paediatric patients, the MAH should submit an updated pop PK model based on additional PK sampling in patients aged 1 month to 6 years from study LOXO-TRK-15003 (SCOUT).

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Of the three studies included in the primary efficacy assessment (Table 23), two included a dose-escalation phase; these trials are described here, although these are also considered main studies.

Study LOXO-TRK-14001

A Phase 1 Study of the oral TRK inhibitor LOXO-101 in adult patients with solid tumours

Methods

Study LOXO-TRK-14001 is an ongoing, multicentre, uncontrolled, open-label Phase 1 dose escalation study in adult patients with advanced solid tumours. There are 2 study periods:

Dose escalation phase (complete, n = 61): patients received larotrectinib dose levels that ranged from 50 mg once daily (QD) to 200 mg twice daily (BID).

Expansion phase (ongoing, n = 9): for patients with documented *NTRK* gene fusion and for patients whom the Investigator believed might benefit from a highly selective TRK inhibitor. All patients received larotrectinib 100 mg BID.

The study recruitment was initiated in May 2014. The clinical protocol has been amended several times with substantial changes to the study design, including changes in inclusion and exclusion criteria, number of patients, dose regimen, schedule of events, concurrent medication, etc.

Rationale for Study Design and Starting Dose

The rat, as the most sensitive species, was used for the calculation of the maximum recommended starting dose. The no-observable-adverse-effect-level (NOAEL) was determined to be 20 mg/kg/day. The severely toxic dose in 10% of animals (STD10) was not established in the 28-day repeat-dose study, as no severe toxicities were induced in the rat. Therefore, the high dose of 200 mg/kg/day was used to calculate the maximum recommended starting dose for Phase 1 of 210 mg/day. The actual starting dose of 50 mg QD represented approximately 25% of this calculated maximum starting dose. Based on preclinical pharmacology experiments with human cancer cells in vitro and in murine xenograft models, the projected range of doses expected to provide inhibition of TRK in tumours was 50 to 400 mg QD or BID.

Dose escalation

The Dose Escalation Phase of the study employed a classical "3+3" design, with 3 to 6 patients to be enrolled in each cohort. Enrolment in the next dose escalation cohort could begin, with SRC approval, provided that > 1 DLT in ≤ 6 patients was not observed.

Patients not receiving 75% of the planned total dose in Cycle 1 (C1) (i.e., who discontinued treatment for reasons unrelated to study drug toxicity or who missed doses due to noncompliance) were considered to have inadequate study drug exposure and were to be replaced. The dose escalation was to stop when ≥ 2 patients within a dose escalation cohort had experienced a dose-limiting toxicity (DLT). Dose escalation decisions were based on C1 safety data. However, the SRC periodically reviewed safety from all treatment cycles. The SRC also periodically reviewed serious adverse events (SAEs) and other safety-related data throughout the conduct of the study.

DLT was pre-defined as any of the following treatment-emergent events occurring in the first 28 days (i.e., in C1):

- Grade 3 or 4 non-haematological toxicity, with the exception of fatigue, asthenia, nausea, or other manageable constitutional symptom.
- Grade 3 or 4 vomiting or diarrhoea that persists for more than 24 hours despite anti-emetics or anti-diarrhoeals.
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding.
- Grade 4 anaemia lasting more than 7 days and not explained by underlying condition.

• Grade 4 neutropenia lasting more than 7 days.
• Any toxicity resulting in discontinuation or dose reduction of treatment (with the exception of symptoms related to progressive disease).

Expansion Cohorts

In a protocol amendment (2.1), two expansion cohorts, 1 cohort for patients with NTRK fusions and 1 cohort for all other patients, were included. In the expansion cohorts, patients were to be treated at the MTD or at a lower dose level selected by the Sponsor as likely to provide clinically meaningful target inhibition. The study drug schedule and treatment assessments for patients enrolled in these 2 expansion cohorts were to be the same as in the Dose-Escalation Phase.

Participants

The main criteria for inclusion in this study were:

- Adult patients with a locally advanced or metastatic solid tumour that has progressed or was nonresponsive to available therapies, are unfit for standard chemotherapy or for which no standard or available curative therapy exists.
- For patients being enrolled into a specific expansion cohort, evidence of an NTRK fusion or tropomyosin receptor kinase (TRK) molecular characteristics as specified for that cohort, such as an amplification, mutation or other alteration that may interfere with TRK signalling as previously determined with prior testing from a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalent certified laboratory. Additionally, patients who, in the opinion and clinical judgement of the local Investigator, may derive benefit from a targeted TRK inhibitor like larotrectinib, may also enrol.
- At least 18 years of age.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 and life expectancy of at least 3 months.
- Adequate hematologic status (absolute neutrophil count (ANC) ≥ 1.5×10^9/L and platelet count ≥ 100.0×10^9/L without growth factors or transfusions), hepatic function (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 2.5 × the upper limit of normal (ULN) or < 5 × ULN with documented liver involvement and total bilirubin < 1.5 × ULN), and renal function (glomerular filtration rate ≥ 30 mL/minute).
- No current or recent (6 months) clinically significant active cardiovascular (CV) disease, including myocardial infarction, cardiomyopathy, or prolonged corrected QT (QTc) interval > 480 milliseconds.
- No current treatment with a strong cytochrome P-450 3A4 (CYP3A4) inhibitor or inducer, and no malabsorption syndrome or other condition affecting PO absorption.

Treatments

Larotrectinib was administered orally (PO), once (QD) or twice daily (BID). Patients received the assigned larotrectinib dose on Day -3 or Day 1, depending on the protocol version (either QD or BID in accordance with the cohort assignment). Cycles were 28 days. Dose escalation was to proceed through the planned dose escalation cohort levels (50 mg QD, 100 mg QD, 100 mg BID, 200 mg QD, 150 mg BID, 200 mg BID) or until the MTD was reached, or until the Sponsor determined, based on available data (safety, clinical activity, and PK exposure), that a suitable dose had been achieved. Dose advancement was overseen by a Safety Review Committee.

Table 30: Larotrectinib (LOXO-101) Dose Levels by Cohort (Study 14001)

Cohort	Single Dose	Frequency	Total Daily Dose
1	50 mg	QD	50 mg
2	100 mg	QD	100 mg
3	100 mg	BID	200 mg
3a[1]	200 mg	QD	200 mg
4	150 mg	BID	300 mg
5	200 mg	BID	400 mg

Abbreviations: BID = twice daily; QD = once daily.

[1]Cohort was opened in parallel with enrollment into Cohort 3 to evaluate PK data for QD dosing versus BID.

Source: Study 14001 CSR, Table 9-4.

Objectives

The study objectives were to determine the safety of oral larotrectinib, including dose-limiting toxicity (DLT), in adult patients with an advanced solid tumour, characterize the pharmacokinetic (PK) properties, to describe antitumor activity, and to identify the maximum tolerated dose (MTD) and/or the appropriate dose of larotrectinib for further clinical investigation.

Endpoints

The primary endpoint of the study was safety, MTD, and recommended dose for further clinical investigation. Secondary endpoints included overall response rate (ORR), duration of response (DOR) and other measures of antitumor efficacy as determined by Investigator (INV) assessment, and PK variables.

Standard safety tests for investigational oncologic agents were employed, including physical examinations (including vital signs, body weight, and performance status), haematology, serum chemistries, urinalysis, 12-lead electrocardiogram (ECG), and adverse events (AEs).

Sample size

According to the SAP, 3 to 6 patients were planned to be enrolled in each dose cohort in the escalation phase, which was deemed to be a safe and conventional approach in dose escalation of a novel oncologic agent. Approximately 20 patients are targeted for each of the 2 expansion cohorts defined: patients bearing the NTRK fusion, and other patients not otherwise specified. Approximately 20 patients per cohort would provide for a preliminary assessment of the antitumor activity. For example, if the observed ORR is high, i.e. greater than 50%, within a cohort, then the corresponding lower limit of a 1-sided exact 90% CI would exclude true response rates that are considered marginal (i.e. less than 30%).

Statistical Methods

Summary statistics were used to present safety data.

The estimate of the ORR was calculated based on crude proportion of patients with best overall response of complete response (CR) or partial response (PR) that were confirmed, using RECIST v1.1, or RANO, as appropriate to tumour type, using Investigator assessment. The estimate of the ORR was to be accompanied by a 1- and 2-sided CIs with various coverage probabilities (e.g., 80%, 95%).

DOR was calculated for patients who achieved CR or PR as their best overall response.

All analyses are made on observed data only, with no imputations for missing values.

Analysis sets for this interim analysis are Safety Analysis Set and Full Analysis Set, which are identical and include all enrolled patients who receive 1 or more doses of larotrectinib.

In the original version of the protocol, PFS at 6 and 12 months was planned to be evaluated, however, omitted in the SAP. The applicant performed this analysis on the request by the Agency.

Results

The first patient was enrolled 12 May 2014.

Conduct of the study

Protocol amendments

Study LOXO-TRK-14001 is an ongoing, multicentre, uncontrolled, open-label Phase 1 dose escalation study in adult patients with advanced solid tumours. The clinical protocol has been amended multiple times with substantial changes to the study design, including selection and number of patients, dose regimen, schedule of events, concomitant medication, etc. In Version 2.1 of the protocol, the primary objective and selection of the study population were adjusted to focus on an enriched biologically complex population and additional tumour types; the number of patients expanded; dosing instructions and some measurements were adjusted. By Version 3.1, the study that previously was described as a Phase 1a (dose-escalation) / 1b (expansion) study is now identified as a Phase 1, the design of the dose-escalation phase was changed to a "standard 3+3 design" and the number of subjects planned decreased, QD dose regimens were added, dose escalation procedure and the schedule of events was updated, as well as the planned efficacy analyses. Version 4.0 of the protocol was implemented after initiation of the LOXO-TRK-15002 and the LOXO-TRK-15003 study, and included, among others, modifications of the dose levels planned, selection of the dose of 100 mg BID in the dose escalation phase of the study (which is the dose chosen for the Phase 2 study), inclusion of liquid formulation and tumour assessment by RANO, updates of the sample size for the expansion cohorts and the planned efficacy analyses, as well as updates of prohibited concomitant medications, schedule of assessments, and further adjustments of inclusion and exclusion criteria. The latest version of the protocol (Version 5.0) is dated September 2017. The major changes in this version are that the patients to be enrolled into the expansion part of the study will have a proven NTRK fusion, and that the sample size for the expansion cohorts is updated.

Considering the explorative nature of the Study LOXO-TRK-14001, the multiple changes of the study design and the type of these changes, the gathered data would normally not be regarded as sufficiently robust for use as pivotal evidence.

Protocol deviations

Significant protocol deviations are defined as deviations to inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment. According to the Interim Clinical Study Report, 23 out of a total of 392 protocol deviations identified were found to be significant and were related to the investigational product (8 patients), informed consent (5), eligibility criteria (4), study procedures (4), and prohibited concomitant medications (2).

Table 31: Significant Protocol Deviations (Study 14001)

Category	Patient(s)	Details
Inclusion/ Exclusion	[redacted]	Enrolled patient does not meet inclusion criteria: (#6, adequate hematologic function as defined by ANC $\geq 1.5 \times 10^9$).
		Enrolled patient does not meet inclusion criteria: (#5, archival or fresh tumor tissue sample).
		Enrolled patient met exclusion criteria: (#10 positive for Hep B surface antibody).
Informed Consent		ICF was not completed accurately by the patient.
		Incorrect (i.e., unapproved or not current) version of the consent was signed by the patient at screening.
		Revised consent was not provided to the patient at the first study visit following receipt of the IRB approval
		Updated version of the ICF was not presented to the patient at first study visit following receipt of the IRB/EC approved ICF.
Investigational Product		IP that was dispensed to patient was deemed "not acceptable for use."
		Patient assigned dose not per protocol. The patient was initially assigned to the 200 mg cohort. However, as an NTRK fusion patient, the recommended Phase 2 dose of 100 mg BID was administered per Sponsor request.
		Patient was allowed to stay on treatment past documented progression preceding protocol version 4.0.
		Drug was held for greater than 7 days for resolution of a TEAE of elevated ALT and AST.
		With Sponsor approval, the patient was allowed to hold and re-start after a TEAE lasting greater than 7 days.
		With Sponsor approval, the patient was allowed to hold and re-start after a TEAE lasting greater than 7-days; also patient was non-compliant with dosing due to missing 7 days of dosing due to insurance issues.
Investigational Product (Cont'd)		Patient was non-compliant with dosing, receiving less than 80% in Cycle 11 (the defined protocol deviation in regards to compliance was less than 80% or greater than 120%). The study protocol allowed dose hold of 7 days; a waiver was granted to allow this patient a longer dose hold for resolution of SAE. The last dose of drug was 12-Feb-17, with drug being held beyond protocol allowed dose hold of 7 days to allow for resolution of SAE (refer to the narrative for Patient 008-063 for additional information). The intent was for the patient to continue treatment upon resolution of SAE, but the patient withdrew consent instead of resuming treatment. Ultimately, patient did not restart dosing and withdrew consent 20-Mar-17.
Restricted Concomitant Medication Change		Patient was treated with a prohibited concomitant medication (clarithromycin, a CYP3A4 inhibitor).
		Patient was treated with a prohibited concomitant medication treatment (prednisone 20 mg QD).
Study Procedures		EOT visit was not completed.
		SAE was not reported within 24 hours of the site becoming aware of the event.

Abbreviations: ANC = absolute neutrophil count; C = Cycle; EC = Ethics Committee; EOT = end-of-treatment; ICF = informed consent form; Hep B = hepatitis B; IP = investigational product; IRB = Institutional Review Board; SAE = serious adverse event.
Source: Study 14001 CSR, Table 10-4 and 10-5

Dose selection

An MTD was not identified. Discontinuation due to AEs was low at all doses (0% in doses 200 mg QD and 150-200 mg BID). The time on treatment cannot be compared across dose cohorts since they consist of different proportions of patients with NTRK fusions (likely to respond).

The Safety review committee (SRC), in consultation with the Sponsor, elected to expand enrolment at 100 mg BID, given the clinical responses already observed at that dose, and in light of pharmacology models suggesting that larotrectinib exposures at this dose were providing sustained target coverage. The rationale for the selection of the 100 mg BID dose for expansion, and consequently for further development, was affected by a transient safety issue regarding a patient at the 150 dose level. The dose level 150 mg BID was subsequently cleared, and also the 200 mg BID cohort did not fulfil MTD criteria with only 1/6 patients experiencing a DLT. The dose selection of 100 mg BID was considered supported by PK data suggesting that the achieved unbound concentration of larotrectinib at Cmin (12 nM) during steady-state at the dose 100 mg BID (n=5) appeared to be greater than the *in vitro* IC50 (range 1 - 10 nM) for inhibition of TRKA, TRKB, and TRKC, and at C_{max} "much greater" than the IC90 for inhibition of all three TRK kinases.

Efficacy

The efficacy results are presented in the section Analysis performed across trials (pooled analyses AND meta-analysis).

Study LOXO-TRK-15003 ("SCOUT")

A Phase 1/2 Study of the Oral TRK Inhibitor LOXO 101 in Paediatric Patients with Advanced Solid or Primary Central Nervous System Tumours

Methods

Study LOXO-TRK-15003 is an ongoing, multicentre, multinational, open-label Phase 1/ 2 study in paediatric patients aged 1 month to 21 years with advanced solid or primary CNS tumours. The study is divided into:

- Phase 1 dose escalation portion (complete, n = 24). Larotrectinib was administered twice daily, treating between 3 and 9 patients at 1 of 5 planned dose levels or until the MTD was reached. When the optimal dose was thus identified, a Phase 1 expansion cohort of up to 18 patients was planned to further define its safety profile.
- Phase 1 dose expansion portion (ongoing, n = 5) to further define the safety profile.
- Phase 2 (ongoing, n = 14). Enrolment is restricted to patients with *NTRK* gene fusion cancer and included 3 selected cohorts of paediatric patients: infantile fibrosarcoma, other extracranial solid tumours, and primary CNS tumours.

The study started in December 2015 and by the data cut-off of 19 February 2018, a total of 43 patients were enrolled, of whom 34 had TRK fusion cancer. The clinical protocol has been amended repeatedly on the global and country level with substantial changes made in the study design, including selection of patient population, eligibility criteria, sample size, dose modification, study duration, retreatment, etc. The latest protocol version is 9.2, dated October 2017. The SAP was written in August 2017 for the purpose of the first interim analysis.

Participants

Main inclusion criteria

- Phase 1:

  Between 1 and 21 years of age with a locally advanced or metastatic solid tumour or primary CNS tumour that had relapsed, progressed, or was nonresponsive to available therapies and for which no standard or available systemic curative therapy existed; **or**

  At least 1 month of age with a malignancy bearing a documented NTRK fusion that had progressed or was nonresponsive to available therapies, and for which no standard or available curative therapy existed; **or**

  Locally advanced infantile fibrosarcoma that would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection

- Phase 2:

  At least 1 month of age with either a locally advanced or metastatic infantile fibrosarcoma; patients with locally advanced infantile fibrosarcoma must otherwise have required disfiguring surgery or limb amputation to achieve a complete surgical resection; **or**

  Between 1 month and 21 years of age with a locally advanced or metastatic solid tumour or primary CNS tumour that had relapsed, progressed, or was nonresponsive to available therapies and for which there was no standard or available systemic curative therapy and with documented NTRK gene fusion

- Karnofsky (16 years and older) or Lansky (less than 16 years) performance score of at least 50

  Measurable or evaluable disease

  Adequate hematologic, hepatic, and renal function (as defined in the protocol)

Exclusion criteria

- Major surgery within 14 days prior to Cycle 1 Day 1

- Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to Cycle 1 Day 1, ongoing cardiomyopathy; current prolonged QTc interval greater than 480 milliseconds

- Active uncontrolled systemic bacterial, viral, or fungal infection

- Malabsorption syndrome or other condition affecting oral absorption

- Current treatment with a strong CYP3A4 inhibitor or inducer (exceptions listed in protocol)

- Pregnancy or lactation

- (Phase 2 only) Prior progression while receiving a tyrosine kinase inhibitor targeting TRK, including entrectinib, crizotinib and lestaurtanib (patients who received a TRK inhibitor for less than 28 days and discontinued for intolerance are eligible)

Treatments

Larotrectinib (LOXO-101, investigational product) was given orally either as a capsule or as a solution twice daily (BID) as continuous dosing. Initially a physiologically-based PK approach (SimCyp) was used to determine an individual dose (in mg/m^2) that factored in age and body surface area (BSA) with the intent of matching the exposure (AUC) of previously tested adult doses that had been deemed safe. For Cohorts 1 (infantile fibrosarcoma) and 2 (other extracranial solid tumours), these adult-equivalent doses were 100 mg BID and 150 mg BID, respectively. The dosing scheme was subsequently changed to a

simple BSA-based approach as further outlined in the protocol. Treatment for an individual patient was to continue until the occurrence of disease progression, unacceptable toxicity, or other reason for discontinuation.

Table 32: Dosing scheme in study LOXO-TRK-15003

Nominal Cohort	Target Larotrectinib Dose [1]	Dosing Algorithm	PK-based Dose Adjustments
1	9.6–55.0 mg/m^2	SimCyp-based	Yes
2	17.3–120.0 mg/m^2	SimCyp-based	Yes
3	100 mg/m^2 BID (with a maximum of 100 mg BID)	BSA-based	No

BID = twice daily; BSA = body surface area; PK = pharmacokinetic; SimCyp® = A physiologically-based PK approach that took into account the patient's age, BSA, and the ontogeny of the larotrectinib clearance pathways to define a dose in mg/m^2 estimated to deliver equivalent exposures to those previously characterized in adults.

[1] For Cohorts 1 and 2, the target was based on dosing calculation tables in Appendix C of the Protocol

Review of PK data from Cohorts 1 and 2 indicated that the SimCyp algorithm resulted in lower exposures in paediatric patients than anticipated. Some patients in these cohorts required several dose increases to achieve the desired exposure. It was concluded that the SimCyp model was not useful and that a simple BSA-based dose would provide more consistent exposures. The overall dosing strategy for this study was to match the exposure in adults, for whom the recommended dose was 100 mg BID. Based on PK analyses, the dose for Cohort 3 (primary CNS tumours) was set at 100 mg/m2 BID (with a maximum of 100 mg BID).

Due to the above-mentioned titrations, Cohorts 1 and 2 contained a heterogeneity of actual doses as expressed in mg/m^2. Hence, this report uses the nomenclature "Cohort 1, Cohort 2, and Cohort 3" to describe the cohorts.

Larotrectinib was provided in various forms for oral dosing as follows:

• Larotrectinib solution was a clear, yellow-to-reddish solution at a concentration of 20 mg/mL, provided to the patient in single-patient amber oval bottles containing 60 mL of solution.

• Larotrectinib capsules of 25 mg (size 2) or 100 mg (size 0) were used for doses of 25 mg or greater. Both capsules were of hard gelatin, white in colour, and distinguishable by size; these were provided in bottles of 72 capsules/bottle.

• Prior to availability of the formulated solution, larotrectinib as a reddish-orange powder was provided for the pharmacist to compound into a 20 mg/mL solution for oral administration. (Three patients enrolled early in the study received this dosage form before being transferred over to the oral solution.)

Objectives and endpoints

Phase 1

The primary objective was to determine the safety and dose-limiting toxicities (DLT) of oral larotrectinib in paediatric patients with advanced solid or primary central nervous system (CNS) tumours. Secondary objectives included pharmacokinetic characterization, identification of maximum tolerated dose (MTD) and/or the appropriate dose of larotrectinib, to describe antitumor activity, and to study pain and health-related quality of life aspects in this patient population.

Phase 2

The primary objective was to determine the overall response rate (ORR) in paediatric patients with an advanced cancer harbouring an NTRK fusion who received larotrectinib. Secondary objectives included

the study of other efficacy parameters including duration of response (DOR), and to further assess the safety and tolerability of larotrectinib.

Sample size

Phase 1 Dose escalation: Up to 6 patients evaluable for safety were to be enrolled in each dose cohort based on a Phase 1 rolling 6 design (Skolnik 2008) with the exception of Cohorts 3, 4, and 5, which could enrol up to 9 patients each in order to fulfil the requirement for at least 3 patients that meet minimum BSA criteria. It was anticipated that up to 36 patients would be required in order to define the MTD or optimal Phase 2 dose of larotrectinib.

Phase 1 Expansion: Following dose escalation, approximately 12-18 patients with specific abnormalities in the NTRK genes or proteins could be enrolled, based on clinical considerations for Phase 1 studies.

Phase 2: Approximately 10 patients were to be enrolled in each of the designated cohorts. The number of patients planned for each Phase 2 cohort was determined largely by feasibility considerations owing to the extreme rarity of paediatric NTRK fusion cancers. Although the planned sample size was limited, it was anticipated that the ORR would be high (≥50%) for each cohort evaluated. If such response rates were observed, than the lower limit of the CI could be used to identify true response rates. For example, if among the 10 patients enrolled within a cohort, there are 5 (50%), 6 (60%), 7 (70%), or 8 (80%) patients with CR or PR, then the 80% CI about this response rate would be (27, 73), (35, 81), (45, 88), or (55, 95), respectively.

Statistical methods

Summary statistics were used to present safety data. The methods of statistical analysis of ORR and DOR were similar to the corresponding analysis in the LOXO-TRK-14001 study. CBR (clinical benefit rate) defined as the sum of patients with either a CR, PR or with stable disease, was analysed similarly.

All analyses were made on observed data only, with no imputations for missing values.

Analysis sets for this interim analysis are Safety Analysis Set and Full Analysis Set, which are identical and include all enrolled patients who receive 1 or more doses of larotrectinib.

No interim analyses were pre-planned and accounted for in the analyses, but the study results are already reported twice.

Results

The first patient was enrolled 16 December 2015.

Forty-three (43) patients were represented in the interim report of the data cut-off of 19 February 2018. All enrolled patients were treated with larotrectinib. Both the Safety and Full Analysis Sets consist of all 43 patients, of whom 28 (65%) were still on treatment at the time of the cut-off date. Among the 15 patients who had discontinued treatment, the most common reason across dose groups was disease progression (7 patients).

Conduct of the study

Protocol amendments

Study LOXO-TRK-15003 is an ongoing, multicentre, multinational, open-label Phase 1/2 study in paediatric patients aged 1 month to 21 years with advanced solid or primary CNS tumours.

The study started in December 2015. The clinical protocol has been amended multiple times on the global and country level with substantial changes made in the study design, including selection of patient population, eligibility criteria, sample size, dose modification, study duration, retreatment, etc. Version

3.0 of the protocol allowed inclusion of patients with congenital mesoblastic nephroma (CMN), and, among other changes, included further refinement of dose modification procedures and clarification of DLT classification. Further dosing modifications were done in Version 4.0.

Major changes were done in Version 5.0, such as change of the study from Phase 1 to Phase 1/2 (i.e. a Phase 2 expansion part was added, planned to include 3 cohorts of patients), and update of the main design elements (e.g., objectives, eligibility criteria, procedures, statistical analysis) of the study to support the change to Phase 1/2. Also, selection of the study population was updated to include patients with locally advanced infantile fibrosarcoma who may require disfiguring surgery or limb amputation. Interim analysis of pharmacokinetic data from Cohorts 1 and 2 informed decision to include a BSA-based dosing algorithm for the subsequent cohorts.

In Version 6.0, the maximum dose in paediatric patients was set be no higher than the recommended Phase 2 dose of 100 mg BID in the adult Phase 2 study, and further clarifications were made about the doses and dose escalation. Version 7.0 revised general treatment procedures and DLT, defined MTD, allowed screen failures to be re-screened.

The major revisions in Version 8.0 were made in the recommended Phase 2 dose, the planned sample size, eligibility criteria (e.g., Phase 1 expansion cohort to enrol paediatric patients with advanced solid or primary CNS tumours with a documented NTRK gene fusion; patients with infantile fibrosarcoma are required to have a documented NTRK fusion by NGS; dose expansion cohort must have a documented NTRK gene fusion; patients with NTRK-fusion positive benign tumours also to be included; patients aged from birth are eligible for inclusion), etc.

The latest global protocol version is 9.0, dated February 2016. In this version there is a change in schedule of assessment cycle 1, and more clarifications regarding eligibility criteria, dosing for newborns, and dose rounding for the oral solution formulation.

Protocol deviations

According to the Interim Clinical Study Report, 8 out of a total of 152 protocol deviations were considered significant, and included 4 eligibility exceptions, and 1 deviation each in the informed consent, study drug, concomitant medication and study procedures (Table 33).

Table 33. Significant Protocol Deviations (Study 15003)

Category	Patient	Details
Eligibility	[redacted]	For these patients with infantile fibrosarcoma, the only available curative option was disfiguring surgery. The original protocol excluded these. Patients were allowed on protocol by Sponsor to avoid surgery (approved by FDA on 3 May 2016, 20 July 2016, and 17 August 2016, respectively).
		Screening ALT was > 1.5x ULN (91 U/L, Grade 1)
Informed consent		Patient underwent study-specific screening procedures after having signed an incorrect version of Informed Consent.
Study drug		Dose given in Cycle 1 was 20% lower than required dose due to error in BSA calculation. Patient received 20 mg rather than 24 mg.
Concomitant medications		Patient received the corticosteroid prednisolone on Day –7 through Day 9, starting higher than the 10 mg/day limit, tapering from 30 to 15 to 7.5 mg.
Study procedures		Patient underwent surgical resection of the primary tumor before the protocol amendment that permitted it (Version 5.0).

Source: Study 15003 CSR, Table 10-3.

Efficacy

The efficacy results are presented in section Analysis performed across trials (pooled analyses AND meta-analysis).

2.5.2. Main study(ies)

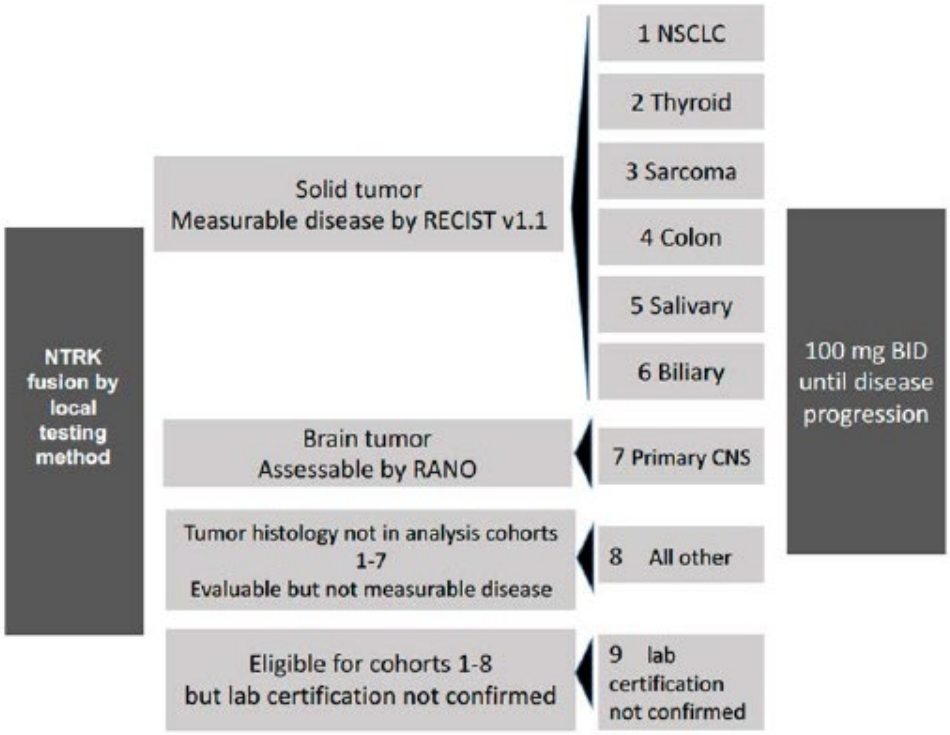
LOXO-TRK-15002 ("NAVIGATE")

A Phase 2 Basket Study of the Oral Human Tropomyosin Receptor Kinase (TRK) Inhibitor Larotrectinib in Subjects with Human Neurotrophic Tyrosine Kinase Receptor (NTRK) Fusion-Positive Tumours

Methods

Study LOXO-TRK-15002 ("study 15002) is an ongoing multicentre, multinational, open label Phase 2 "basket" study in patients aged 12 years and older with recurrent advanced solid tumours with an NTRK1, NTRK2, or NTRK3 gene fusion, as documented by a Clinical Laboratory Improvement Amendments of 1988 (CLIA) or equivalently certified laboratory.

The study included a screening period, a treatment period, a safety follow-up visit, and long-term follow-up (LTFU) assessments. Safety, survival, and subsequent anticancer therapies are tracked in the LTFU period.



Source: Study 15002 protocol, version 7.4, Figure 3-1.

Figure 22: **Study design (Study 15002)**

Study Participants

The following were the diagnosis and main inclusion criteria:

1. Locally-advanced or metastatic malignancy with an NTRK1, NTRK2 or NTRK3 gene fusion, identified through molecular assays as routinely performed at CLIA or other similarly-certified laboratories.

2. Patients must have received prior standard therapy appropriate for their tumour type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.

3. Patients must have had at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST v1.1). Patients without RECIST v1.1 measurable disease (e.g., evaluable disease only) were eligible for enrolment to Cohort 8, regardless of tumour type.

4. Patients in Cohort 7 (primary central nervous system [CNS] tumours) should have met the following criteria:

a. Had received prior treatment including radiation and/or chemotherapy, with radiation completed > 12 weeks prior to Cycle 1 Day 1 (C1D1) of therapy, as recommended or appropriate for that CNS tumour type

b. Had ≥ 1 site of bi-dimensionally measurable disease (confirmed by magnetic resonance imaging [MRI] and evaluable by Response Assessment in Neuro-Oncology Criteria [RANO] criteria), with the size of at least one of the measurable lesions ≥ 1 cm in each dimension and noted on more than one imaging slice

c. Imaging study performed within 28 days before enrolment while on stable dose steroid medication for at least 5 days immediately before and during the imaging study.

5. At least 12 years of age.

6. Eastern Cooperative Oncology Group (ECOG) score of ≤ 3. For those entered into Cohort 7, Karnofsky Performance Status (KPS) of 50.

Treatments

Larotrectinib was administered to patients at 100 mg twice daily (BID) and cycles were in 28-day increments.

Larotrectinib was provided as a hard gelatin capsule in 2 strengths: 25 mg and 100 mg. Both capsule strengths provided were opaque white in colour and were distinguishable by size (capsule sizes 2 and 0, respectively).

Larotrectinib could also be provided as a solution for patients who could not swallow capsules. The solution was provided as a clear, yellow to reddish coloured solution in a concentration of 20 mg/mL.

Objectives and endpoints

The primary objective of the study was to determine the overall response rate (ORR) by independent radiology review (IRC).

Secondary objectives included other efficacy parameters including progression-free survival (PFS), overall survival (OS) and clinical benefit rate (CBR), and to further assess the safety and tolerability of larotrectinib.

Sample size

Up to 18 patients per tumour-specific cohort and up to 100 patients in the Other Tumour NOS cohort were to be included, with an expected total sample size of approximately 226 patients.

For the cancer-specific cohorts (cohorts 1-7), Simon's two-stage design was used to determine whether larotrectinib had sufficient anticancer activity to warrant further development for that tumour type. Enrolment within a cohort was to be terminated early in the event larotrectinib was not sufficiently effective. The decision to terminate or continue enrolment within a cohort was made independently of the other cohorts.

For each cohort, a true ORR of 10% or less was considered insufficient to warrant further study (null hypothesis), whereas a true ORR of 30% or more was considered sufficiently effective (alternative hypothesis). The number of patients evaluated in each stage and the minimum number of responders needed to continue to the next stage were determined based on the optimum version of the aforementioned design, with 80% power and 1-sided significance level of 10%. Based on the above design considerations, up to 7 patients were to be enrolled in each cohort (Stage 1). If no patients were determined to achieve a complete response (CR) or partial response (PR) (confirmed or unconfirmed) within a cohort, then enrolment within that cohort was terminated. Otherwise, 11 additional patients were to be enrolled within the cohort (second stage).

According to the original protocol, the study 15002 was not planned to be pooled with any other study and each cohort was going to be analysed separately. The sample size was planned according to Simon's two-stage design which controls the type I error rate within a cohort, but no multiplicity adjustment for the 7 different cohorts is proposed. Furthermore, there is no type I error control when selected cohorts are pooled.

Randomisation and blinding (masking)

This was a single arm open-label study.

Statistical methods

Analysis set

The Full Analysis Set included all enrolled patients who received at least 1 dose of larotrectinib. The Full Analysis Set was used primarily for the analysis of tumour response and other efficacy-related analyses.

Efficacy Analyses

As originally designed, the primary endpoint was overall response rate (ORR) by independent radiology review. However, in the interim report in this application ORR by Investigator assessment is presented.

No formal statistical tests were performed at the interim analysis of this study. All efficacy analyses were descriptive only and were performed based on the Full Analysis Set.

The point estimates of the ORR were calculated based on the maximum likelihood estimator (i.e., crude proportion of patients with BOR of confirmed CR or PR) based on the Full Analysis Set. The point estimate of ORR was to be accompanied by a 1-sided 90% exact binomial confidence interval (CI) using the Clopper-Pearson method. Additionally, 1-sided 97.5% exact binomial CIs for the ORR have also been presented.

Missing values were not imputed and only observed values were used in data analyses and presentations.

The efficacy results have not been presented based on the Full analysis set as described above. Instead efficacy results have been presented for an "evaluable set".

Results

Recruitment

The first patient was enrolled 13 October 2015. There were study sites in Denmark, France, Ireland, Portugal, Singapore, South Korea, Spain, United Kingdom (UK), and United States (US).

Conduct of the study

Changes to the study and planned analyses that affect the statistical planning and type I error control

Several changes were made to the original protocol dated 23 June 2015.

In the first amendment to the protocol, dated 13 August 2015, the size of cohort 8 was reduced from 100 to 25. In version 5 of the protocol (dated 17 June 2016) the following was added: "*Subjects who do not have any radiological disease assessments after the initiation of LOXO-101, irrespective of reason including death, will be replaced"*. This was deleted again in version 7 of the protocol (dated 24 July 2017), where also a 9th cohort was added for patients where lab certification were not confirmed.

After interaction with national agencies in April 2016, the applicant decided to pool all cohorts except for the CNS tumours cohort for analysis in the MAA. This was not explicitly stated in a protocol amendment for the study. In 2017 the Applicant further changed the strategy for MAA to pooling of data across studies LOXO-TRK-14001, LOXO-TRK-15002 and LOXO-TRK-15003 to serve as the primary efficacy dataset for the MAA. No patients were replaced between version 5 and version 7 of the protocol.

Other protocol changes

In addition to the changes in overall study design described above, many changes to the study protocol were made during the ongoing study as new data emerged, including with regard to patient eligibility criteria, such as age (from adult to 12 years in version 5; to 8 years in version 6.3) and requirements with regard to organ function; addition of study objectives, e.g. quality of life (version 3, and 6.2, paediatric); additional criteria for prior anticancer treatment (version 5); the addition of a cohort 9 for patients where an established assay has detected an NTRK fusion, but laboratory CLIA-equivalent certification has not been confirmed at the time of patient consent (version 7.0), clarifying rules for the reporting of adverse events (version 7.0), change in allowed glucocorticoid doses (version 7.2), addition of optional tumour biopsies at progression (version 7.2), etc.

Outcomes and estimation

Table 34: Overall Response Rate Determined for Confirmed and Unconfirmed Response by tumour cohorts (Study 15002)

Measurable Patients	Cohort 1 (NSCLC) (n = 6)	Cohort 2 (Thyroid) (n = 9)	Cohort 3 (Sarcoma) (n = 12)	Cohort 4 (Colorectal) (n = 6)	Cohort 5 (Salivary) (n = 14)	Cohort 6 (Biliary) (n = 2)	Cohort 7 (Primary CNS) (n = 3)	Cohort 8 (Other) (n = 11)	Total (N = 63)
Number of Evaluable Patients [a]	5	9	12	6	13	2	2	9	58
Overall Response Rate (CR+PR, Confirmed or pending confirmation) (n, %) [b]	5 (100.0)	6 (66.7)	10 (83.3)	3 (50.0)	11 (84.6)	1 (50.0)	0	4 (44.4)	40 (69.0)
90% CI (%) [c]	(63.1, -)	(40.1, -)	(61.4, -)	(20.1, -)	(64.0, -)	(5.1, -)	0	(21.0, -)	(59.9, -)
97.5% CI (%) [c]	(47.8, -)	(29.9, -)	(51.6, -)	(11.8, -)	(54.6, -)	(1.3, -)	0	(13.7, -)	(55.5, -)

Abbreviations: CI = confidence interval; CNS = central nervous system; CR = complete response; NSCLC = non-small cell lung cancer; PR = partial response.

Note: The table is based on the Investigator assessment of response in the subgroup of the Full Analysis Set, N = 63.

Percentage is calculated using the number of evaluable patients as the denominator.

a) Evaluable patients are defined as patients with measureable disease at baseline and with evaluable post-baseline assessments.

b) Overall response rate (ORR) (%) is defined as the proportion of patients with BOR of confirmed or unconfirmed CR or PR by RECIST v1.1 or RANO, as appropriate to tumor type. CR or PR is confirmed by a repeat assessment no less than 28 days.

c) One-sided 90% or 97.5% exact binomial CI for ORR is calculated using Clopper-Pearson method.

Data cut-off 19 February 2018;

Further efficacy results are presented in section Analysis performed across trials (pooled analyses AND meta-analysis).

Summary of main studies

The following tables summarise 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 35: Summary of efficacy for trial 14001

Title: A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Adult Patients with Solid Tumors		
Study identifier	Internal Study Number: LOXO-TRK-14001 EudraCT number: n.a. ClinicalTrials.gov Identifier: NCT02122913	
Design	Multicenter, Phase 1, open-label, 3 + 3 dose escalation study in adult patients with advanced solid tumours.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Dose escalation through planned dose escalation cohort levels, until MTD reached, or suitable dose had been achieved Not applicable Individual patients continued larotrectinib until disease progression, unacceptable toxicity, or other reason for treatment discontinuation (also applies to dose escalation)
Hypothesis	None, descriptive analysis only	
Treatment groups	Cohort 1	Single dose of 50 mg larotrectinib, QD, total daily dose of 50 mg
	Cohort 2	Single dose of 100 mg, QD, total dose of 100 mg
	Cohort 3	Single dose of 100 mg, BID, total daily dose of 200 mg
	Cohort 3a	Single dose of 200 mg, QD,

			total daily dose of 200 mg
	Cohort 4		Single dose of 150 mg, BID, total daily dose of 300 mg
	Cohort 5		Single dose of 200 mg, BID, total daily dose of 400 mg
	NTRK fusion patients		Patients with documented NTRK fusion among all cohorts
	Non-NTRK fusion patients		Patients without documented NTRK fusion among all cohorts
Endpoints and definitions	Primary: Maximum Tolerated Dose	MTD	MTD would have been considered to be the dose level immediately below that which results in a DLT (defined in the study protocol) incidence of 33% or higher. A MTD was not established.
	Primary: Recommended dose for further investigation	Recommended dose	Determine the appropriate dose of larotrectinib for further clinical investigation
	Secondary:Overall Response Rate	ORR	As assessed using RECIST 1.1 or RANO, as appropriate to tumour type
	Secondary: Duration of Response	DOR	Determined for patients with BOR of confirmed CR or PR as the number of months from the start of CR or PR (whichever response was recorded first) to the first date that recurrent or progressive disease is documented, or death
	Other: Best Overall Response	BOR	Best overall response (BOR) of confirmed CR or PR as determined by the treating Investigator using RECIST v1.1 or RANO criteria, as appropriate to tumour type
Database lock	30 JUL 2018		

Results and Analysis

Analysis description	**Interim Analysis**		
Analysis population and time point description	NTRK fusion patients contributing to ePAS2 and SAS3, as well as non-NTRK fusion patients 30 JUL 2018		
Descriptive statistics and estimate variability	Patient group	NTRK fusion patients contributing to ePAS2 and SAS3	Non NTRK fusion patients
	Number of subjects	8	62
	ORR (n, %)	7 (88%)	1 (2%)
	95% CI	(47%,100%)	(0%, 9%)
	DOR (months, median)	Not estimable, minimum >17.2 months, maximum >38.7 months	3.7 (n=1)
	BOR (n, %) CR, confirmed PR, confirmed	 2 (25%) 5 (63%)	 0 1 (2%)
Effect estimate per comparison	Not applicable, uncontrolled study		

Notes	8 Patients from this study contributed to the pre-specified primary efficacy evaluation based on primary analysis set (PAS) population of the integrated efficacy data pool. Data are given as reported in the interim clinical study report based on investigator assessment, as opposed to the pooled data reported in the clinical summary documents submitted, which are based on central assessment.

Table 36: Summary of efficacy for trial 15002

Title: A Phase 2 Basket Study of the Oral TRK Inhibitor Larotrectinib in Subjects with NTRK Fusion-Positive Tumors		
Study identifier	Internal Study Number: LOXO-TRK-15002 EudraCT number: 2015-003582-28 ClinicalTrials.gov Identifier: NCT02576431	
Design	Multicentre, Phase 2, open-label "basket" study in patients 12 years of age or older with an advanced cancer bearing an NTRK gene fusion.	
	Duration of main phase:	Until disease progression (PD), unacceptable toxicity, patient withdrawal of consent, or death. Patients with PD were allowed to continue larotrectinib if deriving clinical benefit and approved by the Sponsor.
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	None, uncontrolled study	
Treatment groups	Cohort 1: Non-Small Cell Lung Cancer	100 mg BID via capsule or oral solution continuously in 28 day cycles until disease progression, unacceptable toxicity, subject withdrawal of consent or death
	Cohort 2: Thyroid	100 mg BID via capsule or oral solution continuously in 28 day cycles until disease progression, unacceptable toxicity, subject withdrawal of consent or death
	Cohort 3: Sarcoma	100 mg BID via capsule or oral solution continuously in 28 day cycles until disease progression, unacceptable toxicity, subject withdrawal of consent or death
	Cohort 4: Colorectal	100 mg BID via capsule or oral solution continuously in 28 day cycles until disease progression, unacceptable toxicity, subject withdrawal of consent or death
	Cohort 5: Salivary gland	100 mg BID via capsule or oral solution continuously in 28 day cycles until disease progression, unacceptable toxicity, subject withdrawal of consent or death
	Cohort 6: Biliary	100 mg BID via capsule or oral solution continuously in 28 day cycles until disease progression, unacceptable toxicity, subject withdrawal of consent or death
	Cohort 7: Primary CNS	100 mg BID via capsule or oral solution continuously in 28 day cycles until disease progression, unacceptable toxicity, subject withdrawal of consent or death
	Cohort 8: Other tumours not otherwise specified	100 mg BID via capsule or oral solution continuously in 28 day cycles until disease progression, unacceptable toxicity, subject withdrawal of consent or death
	Cohort 9: Cohorts 1-8 with documented NTRK fusion but without Clinical Laboratory Improvement Amendments (CLIA)-equivalent laboratory certification at the time of patient	100 mg BID via capsule or oral solution continuously in 28 day cycles until disease progression, unacceptable toxicity, subject withdrawal of consent or death

	consent		
Endpoints and definitions	Primary: Overall Response Rate	ORR	As assessed using RECIST 1.1 or RANO, as appropriate to tumour type
	Secondary: Best Overall Response	BOR	Best overall response (BOR) of confirmed CR or PR as determined by the treating Investigator using RECIST v1.1 or RANO criteria, as appropriate to tumour type
	Secondary: Duration of Response	DOR	Determined for patients with BOR of confirmed CR or PR as the number of months from the start of CR or PR (whichever response was recorded first) to the first date that recurrent or progressive disease is documented, or death
	Secondary: Clinical Benefit Rate	CBR	Proportion of patients with BOR of confirmed CR, PR, or stable disease (SD) lasting 16 or more weeks following the initiation of larotrectinib
	Secondary: Progression-Free Survival	PFS	Number of months from initiation of larotrectinib to the earlier of disease progression or death due to any cause
	Secondary: Overall Survival	OS	Number of months from the initiation of larotrectinib to the date of death due to any cause
Database lock	30 JUL 2018		

Results and Analysis

Analysis description	**Interim Analysis**	
Analysis population and time point description	Patients contributing to ePAS2 and SAS3 as of 30 JUL 2018	
Descriptive statistics and estimate variability	Patient group	Patients contributing to ePAS2 and SAS3
	Number of subjects	62
	BOR (n, %) CR, confirmed PR, confirmed	 7 (11%) 35 (56%)
	ORR, confirmed responses only (n,%)	42 (68%)
	95% CI	(55, 79)
	DOR (months, median and range)	19.8 (n=42) (2.1+, 31.3+)
	95% CI	(13.3, not estimable)
	PFS (months, median and range)	-
	95% CI	-
	OS (months, median and range)	-
	95% CI	-
Effect estimate per comparison	Not applicable, uncontrolled study	
Notes	35 Patients from this study contributed to the pre-specified primary efficacy	

	evaluation based on primary analysis set (PAS) population of the integrated efficacy data pool. An additional 9 patients contributed to the extended primary analysis set (ePAS) population of the integrated efficacy data pool. Compared to the ePAS, the ePAS2 dataset includes 14 additional patients from this study. The study also contributes 4 patients to the SAS3 dataset. Data are given as reported in the interim clinical study report based on investigator assessment, as opposed to the pooled data reported in the clinical summary documents submitted, which are based on central assessment.

Table 37: Summary of efficacy for trial 15003

Title: A Phase 1/2 Study of the Oral TRK Inhibitor LOXO-101 in Pediatric Patients with Advanced Solid or Primary Central Nervous System Tumors			
Study identifier	Internal Study Number: LOXO-TRK-15003 EudraCT number: 2016-003498-16 ClinicalTrials.gov Identifier: NCT02637687		
Design	Multicentre, Phase 1/2, open-label, dose escalation study in paediatric patients with advanced solid or primary CNS tumours		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Dose escalation through planned dose escalation cohort levels, until MTD reached, or suitable dose had been achieved Not applicable Individual patients continued larotrectinib until disease progression, unacceptable toxicity, or other reason for treatment discontinuation (also applies to dose escalation)
Hypothesis	None, descriptive evaluation only		
Treatment groups	Cohort 1		Target larotrectinib dose 9.6-55.0 mg/m^2, PK-based dose adjustments
	Cohort 2		Target larotrectinib dose 17.3-120.0 mg/m^2, PK-based dose adjustments
	Cohort 3		100 mg/m^2 BID, no PK-based dose adjustments
	NTRK fusion patients		Patients with documented NTRK fusion among all cohorts
	Non-NTRK fusion patients		Patients without documented NTRK fusion among all cohorts
Endpoints and definitions	Maximum Tolerated Dose	MTD	MTD would have been considered to be the dose level immediately below that which results in a DLT (defined in the study protocol) incidence of 33% or higher. A MTD was not established.
	Recommended dose for further investigation	Recommended dose	Determine the appropriate dose of larotrectinib for further paediatric investigation
	Primary: Overall Response Ratio	ORR	ORR was calculated based on the crude proportion of patients with best overall response of complete response (CR) or partial response (PR)
	Secondary: Duration of Response	DOR	Determined for patients with BOR of confirmed CR or PR as the number of months from the start of CR or PR (whichever response was recorded first) to the first date that recurrent or progressive disease is documented, or death
	Other: Best Overall Response	BOR	Best overall response (BOR) of confirmed CR or PR as determined by the treating Investigator using RECIST v1.1 or RANO

			criteria, as appropriate to tumour type
Database lock	30 JUL 2018		
Results and Analysis			
Analysis description	**Interim Analysis**		
Analysis population and time point description	NTRK fusion patients contributing to ePAS2 and SAS3, as well as non-NTRK fusion patients 30 JUL 2018		
Descriptive statistics and estimate variability	Patient group	NTRK fusion patients contributing to ePAS2 and SAS3	Non-NTRK fusion patients
	Number of subjects	32	9
	ORR (n, %)	26 (81%)	0
	95% CI	(64, 93)	(-, -)
	BOR, based on all 34 patients (n, %) CR, confirmed Surgical complete response PR, confirmed	 7 (22%) 1 (3%) 18 (56%)	 0 0 0
	DOR (months, median and range)	Not estimable (n=26) (>1.6, >26.7)	-
Effect estimate per comparison	Not applicable, non-controlled study		
Notes	12 Patients from this study contributed to the pre-specified primary efficacy evaluation based on primary analysis set (PAS) population of the integrated efficacy data pool. An additional 9 patients contributed to the extended primary analysis set (ePAS) population of the integrated efficacy data pool. Compared to ePAS, the ePAS2 dataset includes an additional 6 patients from this study. The study also contributes 5 patients to the SAS3 dataset. Data are given as reported in the interim clinical study report based on investigator assessment, as opposed to the pooled data reported in the clinical summary documents submitted, which are based on central assessment.		

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

Three larotrectinib clinical studies represent the primary efficacy basis for larotrectinib. The first patients were enrolled 12 May 2014 (Study 14001), 13 October 2015 (Study 15002) and 16 December 2015 (Study 15003).

The studies are ongoing and this application is based on interim data that have been pooled from the three studies. The contribution from each study is shown in Table 39 and is further addressed under Numbers analysed below (p. 107).

Results from three different data cut-off dates for the pooled analyses have been presented based on consequently different numbers of patients as shown in Table 38.

Results for an additional patient population, which is encompassed by the indication, are also presented. The pooled primary analysis populations excluded patients from the pivotal studies who had primary CNS tumours. These patients, pooled from Studies 15002 and 15003, comprise the Supplemental analysis set 3 (SAS3).

Table 38: Pooled populations; cut-off dates and number of patients (N)

Study population	N	Data cut-off	Comment
Primary analysis set (PAS)	55	Updated 19 February 2018	Used for FDA approval in the US (17 July 2017)
Extended primary analysis set (ePAS)	73	19 February 2018 30 July 2018	Submitted at initial MAA Submitted at CHMP request in responses to questions
Second extended primary analysis set (ePAS2)	93	30 July 2018	Submitted at CHMP request in responses to questions
Supplemental analysis set 3 (SAS3)	9	30 July 2018	Primary CNS tumours

Table 39: Clinical efficacy and safety studies with contribution to analysis populations

Study No., Dates, Location	Study Design and Objectives	Larotrectinib Doses and Formulation	Total no. Patients Receiving Larotrectinib	Patients with NTRK Gene Fusion	Patients in Primary Efficacy Analyses		
					PAS	SAS3	ePAS2
LOXO-TRK-14001 MAY 2014–data as of 30 JUL 2018. Study ongoing. US 8 sites	Multicentre, Phase 1, open-label, dose escalation (5 planned dose cohorts with 3 to 6 patients per cohort) and dose expansion study (2 planned cohorts) in adult patients with advanced solid tumours. Objectives are to characterize safety and dose-limiting toxicity, MTD / or appropriate dose of larotrectinib for further study, and to characterize its PK properties and antitumour activity (overall response rate and other efficacy parameters).	50–200 mg/day (QD or BID) Opaque white gelatin capsules of 25 mg and 100 mg strengths or oral solution	72	10	8	0	8
LOXO-TRK-15002 OCT 2015–data as of 30 JUL 2018. Study ongoing. US, EU, Singapore, South Korea 22 sites	Multicentre, Phase 2, open-label "basket" study in patients 12 years of age or older with an advanced cancer bearing an NTRK gene fusion. The study includes 8 cohorts of patients with tumours bearing somatic NTRK gene fusions, including NSCLC, thyroid cancer, sarcoma, colorectal cancer, salivary gland cancer, biliary cancer, primary CNS tumours, and a cohort that enrols patients of all other histologic types or patients without measurable disease. The primary objective is to determine the overall response rate and secondary objectives are to determine other efficacy parameters and to further assess the safety and tolerability of larotrectinib. Exploratory objectives include determination of the relationship between PK and drug effects, including efficacy and safety.	100 mg BID Opaque white gelatin capsules of 25 mg and 100 mg strengths or oral solution	82	82	35	4	58

Study No., Dates, Location	Study Design and Objectives	Larotrectinib Doses and Formulation	Total no. Patients Receiving Larotrectinib	Patients with NTRK Gene Fusion	Patients in Primary Efficacy Analyses		
					PAS	SAS3	ePAS2
LOXO-TRK-15003 DEC 2015–data as of 30 JUL 2018. Study ongoing. US, EU, Australia 17 sites	Multicentre, Phase 1/2, open-label, study in paediatric patients with advanced solid or primary CNS tumours. Study has 2 phases: Phase 1, a sequential-cohort, dose escalation study to identify the MTD dose, and Phase 2, treatment with larotrectinib in 3 cohorts of paediatric patients with IFS, other extracranial solid tumours, and primary CNS tumours. The primary objective is to characterize safety and dose-limiting toxicity, and secondary objectives are to characterize PK, identify the MTD/ or appropriate dose of larotrectinib for further study, to describe antitumour activity (overall response rate [primary endpoint] and other efficacy parameters) and pain and health-related quality of life.	Dosing based on adult equivalent of 100 or 150 mg BID, then 100 mg/m^2 BID (with a maximum of 100 mg BID) Actual doses administered ranged from 27.3 to 120.0 mg/m^2 BID Capsules (25 mg and 100 mg) or 20 mg/mL solution. Opaque white gelatin capsules of 25 mg and 100 mg strengths or oral solution	54	45	12	5	27

Abbreviations: BID = twice daily; CNS = central nervous system; ePAS = extended primary analysis set; EU = European Union; IFS = infantile fibrosarcoma; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; NTRK = human neurotrophic tyrosine kinase; PAS = primary analysis set; PK = pharmacokinetics; QD = once daily; US = United States

Methods

Study Participants

See eligibility criteria for inclusion for the individual studies in sections above.

Studies 14001 and 15003 included patients with or without documented NTRK gene fusions while eligibility criteria for the Phase 2 study 15002 required all patients to have an NTRK gene fusion. Study 14001 was performed in adults, Study 15003 in paediatric patients, and Study 15002 in adults and adolescents.

Patients included in all studies were required to have a locally advanced or metastatic solid tumour (i.e. carcinoma or sarcoma). Primary CNS malignancy was specifically mentioned and allowed Studies 15002 and 15003. Patients must have received prior standard therapy or would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy (Study 15002); or must have progressed on prior therapy or was nonresponsive to available therapies and for which no standard or available systemic curative therapy existed (Studies 14001 and 15003); or, for infantile fibrosarcoma, would require disfiguring surgery or limb amputation to achieve a complete surgical resection (Study 15003).

Thus, Study 15002 appears to have somewhat less restrictive inclusion criteria in terms of prior therapy compared to the phase 1/2-studies, since progression on prior therapy was not required. This could

encompass 1st line treatment. Also the wording in the inclusion criteria for studies 14001 and 15003 "for which no standard or available systemic curative therapy exists" appears open for any line of treatment in patients with metastatic tumours, since these are generally not considered curative by any treatment modality. With regard to locally advanced tumours, it is often at least theoretically possible that the tumour might become resectable after effective systemic therapy and thus curable.

Treatments

Larotrectinib has been administered in two different forms: capsule or oral solution.

The target dose for this application is Vitrakvi (larotrectinib) 100 mg BID (adults) or 100mg/m2 BID (paediatric patients, not to exceed adult dose), continuously in 28-day cycles, until disease progression or intolerable toxicity. However, as patients from dose-finding studies are included in the pooled efficacy analysis populations, not all patients received this dose, see Table 64.

It is noted that in at least two of the studies (14001 and 15002) patients with progressive disease were allowed to continue larotrectinib if, in the opinion of the Investigator, the patient was deriving clinical benefit from continuing study drug and continuation of treatment was approved by the Sponsor.

Objectives and endpoints

Table 40. Efficacy Endpoints by Study

	LOXO-TRK-14001	LOXO-TRK-15002	LOXO-TRK-15003	
			Phase 1	Phase 2
Overall response rate investigator assessment	Secondary	Primary	Secondary	Primary
Duration of response	Secondary	Secondary	Secondary	Secondary
Best overall response	Secondary	Secondary		Secondary
Clinical benefit rate		Secondary		
Progression-free survival		Secondary		
Overall survival		Secondary		
Quality of life		Exploratory	Secondary	

Source: SCE, Table 1-4.

Across the 3 studies, disease assessment was performed by computed tomography (CT), positron emission tomography (PET), and/or magnetic resonance imaging (MRI) performed at screening, every other cycle on or around day 1 of odd-numbered cycles, and at the end-of-treatment.

In all 3 studies, tumour response criteria were based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for non-CNS solid tumours and Response Assessment in Neuro Oncology Criteria (RANO) for CNS tumours.

In Study LOXO-TRK-15002, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ5D5L) or Pediatric Quality of Life Inventory (PedsQL) were used as appropriate for the patient's age, and in Study LOXO-TRK-15003, the PedsQL Infant Scale was used for infants 1–24 months of age and the PedsQL 4.0 Generic Core Scale for patients 25 months of age and greater. Quality of life data were not included in the interim analysis with a data cut-off date of 19 FEB 2018.

It was agreed with the regulatory agencies that interim CSRs for the individual studies would utilize Investigator response assessments until preparation of the final CSRs, but for the SCE an integrated analysis pooling data from all 3 studies would be based on Independent Review Committee (IRC) assessments, although the Investigator assessed endpoints would also be presented.

Pooled analyses

- The primary endpoint for the pooled efficacy analyses was ORR by IRC assessment, defined as the proportion of patients with best overall response of confirmed complete response (CR) or confirmed partial response (PR).

Best overall response was defined as the best response designation as of the data cut-off date for each patient recorded between the date of the first dose of larotrectinib and the date of documented disease progression per RECIST v1.1, the date of subsequent therapy or cancer related surgery, or the data cut-off date, whichever occurred first. Patients who underwent surgical resection on therapy with no viable tumour cells and negative margins on postsurgical pathology report were considered a CR by surgery/pathology.

The primary analysis was based on the time point responses and the best overall responses in the PAS recorded by the IRC. In addition, best overall responses were evaluated in the SAS1-IRC and ePAS. Change in tumour burden was calculated for each patient in ePAS as the percentage change from baseline in the sum of diameters of target tumour lesions at each time point. The best tumour burden change was summarized descriptively by calculating the median and interquartile range across patients. A waterfall plot was used to graphically depict tumour burden changes.

Secondary endpoints the pooled analyses:

- ORR based on Investigator assessment for patients with non-CNS primary tumours using RECIST v1.1 criteria (confirmation of response was required)
- Time to response and time to best response
- Duration of response
- Time on treatment
- Disease-control rate
- Progression-free survival (PFS) and PFS rate at 6 and 12 months after initiation of larotrectinib
- Overall survival (OS) and survival rate at 12 months after initiation of larotrectinib.

The IRC assessments served as the principal data source for time to response, time to best response, duration of response, disease control rate, and PFS for the PAS, SAS1-IRC, and ePAS.

Following CHMP request, data from an extended follow-up and a consequently larger pooled analysis population, ePAS2, has been submitted.

Sample size

Under the primary efficacy analysis described in the SAP, a ORR of ≥50% was hypothesized when larotrectinib was administered to patients with TRK fusion cancer. A sample size of 55 patients was estimated to provide 80% power to achieve a lower boundary of the 2-sided 95% exact binomial confidence interval (CI) about the estimated ORR exceeding 30%.

Ruling out a lower limit of 30% for ORR was considered clinically meaningful and consistent with the estimated response rates seen with approved targeted therapies in genetically-defined patient populations who have progressed on prior therapies. Under the primary analysis, the lower limit of the 95% CI would exceed 30% when the estimated ORR was 46% or greater (Clopper-Pearson method).

The SAP for the pooled analysis was dated 15 August 2017. The applicant was asked to clarify how many patients were already included in the studies at that time and for how many of those patients response status had already been evaluated. The Applicant responded that as of 15 AUG 2017, 81 patients had been enrolled into the studies of which 52 patients had response assessed by investigators.

Randomisation and blinding (masking)

All trials in the pooled analysis were open-label and non-randomised.

Statistical methods

Primary Analysis Set

The Primary Analysis Set (PAS) includes the first 55 patients (paediatrics and adults) enrolled across clinical studies LOXO-TRK-14001, -15002, and -15003 who meet the following criteria:

1. Documented NTRK fusion as determined by local testing
2. Non-CNS primary tumour with 1 or more measurable lesions at baseline as assessed by RECIST 1.1
3. Received 1 or more doses of larotrectinib

All patients meeting the criteria listed above were ordered chronologically (from earliest to latest) based on the date larotrectinib was first administered. The first 55 patients from this list are included in the PAS.

Missing Data

For data summarized over time by visit, no imputations were performed on missing data. All analyses will be based on observed data only. The effective sample sizes at each assessment visit will be based on the total number of patients with non-missing data for the parameter of interest at that visit.

Primary Analysis

The data cut-off for the primary analysis was 17 July 2017, approximately 6 months after enrolment of the 55th patient in the PAS. This data cut-off was determined so that the majority of patients in the PAS would have at least 6 months of follow-up after the initiation of larotrectinib. The data cut-off was applied uniformly across studies and all analyses.

The point estimate of the ORR was calculated based on the maximum likelihood estimator (i.e., crude proportion of patients in the PAS with best overall response of confirmed CR or confirmed PR). The point estimate was accompanied by a 2-sided 95% exact binomial CI using the Clopper-Pearson method. The effectiveness of larotrectinib was demonstrated if the lower limit of the 2-sided 95% CI exceeded 30%. Secondary calculations were provided for ORR based on the subset of patients in the PAS with IRC-confirmed measurable disease. Heterogeneity of the estimated ORR by study was evaluated based on the quantity I^2, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins 2003). Values of I^2 lie between 0% and 100%. A value of 0% indicates no observed heterogeneity; larger values of I^2 show increasing heterogeneity.

Notably, the exclusion of CNS-tumours introduces a bias in the estimate. The restriction to the first 55 patients is arbitrarily chosen. Analysing observed data only is not in accordance with the ITT principle. An analysis of ORR using the Full Analysis Set in the denominator were presented as response to questions, and showed somewhat lower estimates of ORR. The result of the heterogeneity evaluation between studies has been provided in the responses showing substantial heterogeneity across studies. Also, considering that the primary endpoint is a crude proportion of responses, a sensitivity analysis utilizing tumour type as a random factor were performed on the pooled data and were provided with the response to questions. This analysis gives slightly lower estimates than the crude rates presented previously.

The analysis presented by the applicant was based on a post hoc pooling of cohorts and of studies and exclusion of one cohort. It is noted that the initial decision to transition to the pivotal pooled design, 10 patients had been sufficiently studied for efficacy. Thus, 45 patients had been recruited prospectively as

part of the initial primary analysis population, PAS (n= 55). The three studies include 5, 8 and 7 cohorts (cancer types) respectively and this gives a large number of possible selections of subsets of one or more cohorts to pool, whereof only one was presented in primary analysis (i.e. the pooled analysis without CNS). In order to illustrate the uncertainties and bias introduced by the applicant's approach, the applicant was asked to present the distribution of ORR estimates resulting from all possible selections of subsets of one or more cohorts. The resulting analysis is presented below (Figure 22, Table 41).

The requested analyses on possible selections of subsets has been performed using the 30 JUL 2018 cut-off database. The analyses used the data from 102 patients: in the ePAS2 (N=93) and the SAS3 (N=9). The analysis uses IRC assessed response data for the patients in the ePAS2 and investigator assessed response data for patients in SAS3. Overall, 19 cohorts were considered in the analysis. Of these, 5 cohorts were included from Study LOXO-TRK-14001, 8 from Study LOXO-TRK-15002, and 6 from Study LOXO-TRK-15003. The Overall Response Rate (ORR) was calculated for all possible selections of subsets of one or more cohorts (number of possible selections: 2^19 - 1 = 524 287).

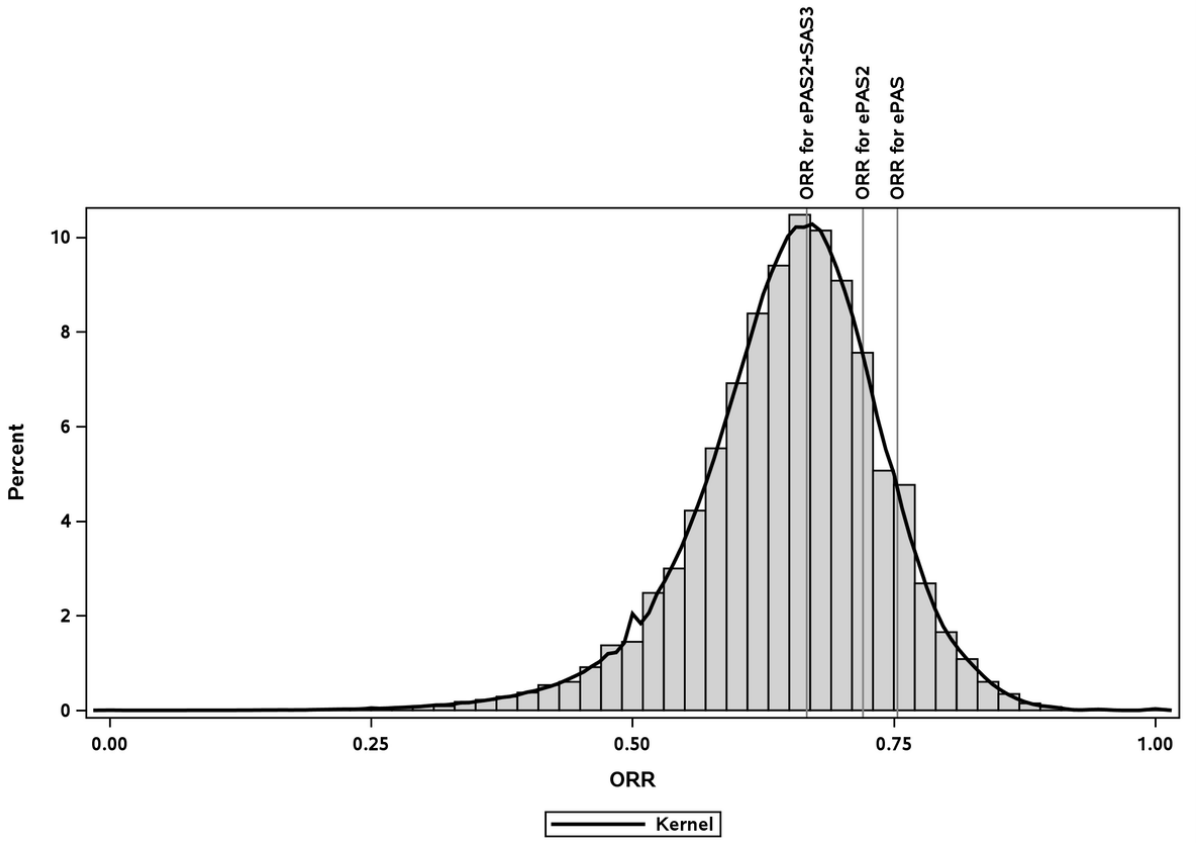


Figure 23: Histogram for all combinations of the 19 cohorts for ORR (ePAS2 + SAS3)

Table 41: Descriptive statistics of all combinations of the 19 cohorts for ORR (ePAS2 + SAS3)

	n	Mean	SD	Min	P5	P25	Median	P75	P95	Max
ORR	524287	0.64967	0.08914	0.0000	0.50000	0.60000	0.65686	0.70769	0.78125	1.0000

Source: Table 1021

All possible selections of cohorts from the three studies have been analysed. The estimated ORR in the ePAS population is in the upper end (the 90th percentile) of the distribution of possible estimates indicating a possible selection bias. On the other hand, a large majority of all possible ORR estimates are above 50% indicating a true effect of a relevant magnitude.

Results

Baseline data

Table 42: Demographics by study and in the pooled study population (ePAS)

	LOXO-TRK-14001			LOXO-TRK-15002	LOXO-TRK-15003			ePAS
	TRK	Non-TRK	Total	TRK	TRK	Non-TRK	Total	TRK
N	8	62	70	63	34	9	43	73
Age, years								
N	8	62	70	63	34	9	43	73
Median	48.0	61.0	59.5	57.0	4.2	13.8	5.3	41.0
Range	28-66	19-82	19-82	6-79	0.1-19.9	3.0-17.6	0.1-19.9	0.1-76.0
Overall age group, n (%)								
< 1 year	0	0	0	0	9 (26)	0	9 (21)	6 (8)
1–5 years	0	0	0	0	12 (35)	2 (22)	14 (33)	8 (11)
6–11 years	0	0	0	1 (2)	6 (18)	1 (11)	7 (16)	4 (5)
12–15 years	0	0	0	2 (3)	4 (12)	4 (44)	8 (19)	3 (4)
16-17 years	0	0	0	0	1 (3)	2 (22)	3 (7)	0
18–44 years	4 (50)	8 (13)	12 (17)	17 (27)	2 (6)	0	2 (5)	17 (23)
45–64 years	3 (38)	35 (56)	38 (54)	25 (40)	0	0	0	20 (27)
65–74 years	1 (13)	16 (26)	17 (24)	12 (19)	0	0	0	13 (18)
≥ 75 years	0	3 (5)	3 (4)	6 (10)	0	0	0	2 (3)
Sex, n (%)								
Male	7 (88)	28 (45)	35 (50)	34 (54)	17 (50)	5 (56)	22 (51)	38 (52)
Female	1 (13)	34 (55)	35 (50)	29 (46)	17 (50)	4 (44)	21 (49)	35 (48)
Race, n (%)								
White	8 (100)	50 (81)	58 (83)	44 (70)	22 (65)	2 (22)	24 (56)	50 (68)
Black	0	8 (13)	8 (11)	5 (8)	0	1 (11)	1 (11)	3 (4)
Asian	0	0	0	4 (6)	1 (3)	1 (11)	2 (5)	3 (4)
Mixed/Other/Unknown	0	4 (6)	4 (6)	10 (16)	11 (32)	5 (56)	16 (37)	17 (23)
Ethnicity, n (%)								
Non-Hispanic	7 (88)	53 (85)	60 (86)	49 (78)	22 (65)	4 (44)	26 (60)	51 (70)
Hispanic/Latino	1 (13)	6 (10)	7 (10)	2 (3)	6 (18)	4 (44)	10 (23)	7 (10)
Other/Unknown	0	3 (5)	3 (4)	12 (19)	6 (18)	1 (11)	7 (16)	15 (21)
Body weight (kg)								
N	8	61	69	62	34	9	43	72
Median	76.1	79.5	79.2	69.5	17.1	34.2	19.9	60.9
Range	48-106	43-177	43-177	23-154	4.2-72	15-83	4.2-83	4.2-153.5
Height (cm)								
N	8	61	69	60	34	9	43	70
Median	176.7	168.9	170.0	169.5	103.9	147.5	111.5	164.5
Range	161-185	151-196	151-196	120-194	52-183	101-172	52-183	54.5-194.0

Shaded columns are the TRK fusion-positive subgroups and analysis population, pertinent to the sought indication.
Abbreviation: ePAS = expanded primary analysis set; TRK = tropomyosin receptor kinase (fusion cancer).

Table 43: Demographics in the pooled primary study population (ePAS2) and primary brain tumour population (SAS3)

Characteristic	ePAS2 (N=93)	SAS3 (N=9)
Sex		
Male	49 (53%)	5 (56%)
Female	44 (47%)	4 (44%)
Race		
White	65 (70%)	8 (89%)
Other	14 (15%)	0 (0%)
Asian	4 (4%)	0 (0%)
Black or African American	4 (4%)	1 (11%)
Not Reported	3 (3%)	0 (0%)
American Indian or Alaska Native	1 (1%)	0 (0%)
Multiple	1 (1%)	0 (0%)
Native Hawaiian or Other Pacific Islander	1 (1%)	0 (0%)
Ethnicity		
Not Hispanic or Latino	68 (73%)	8 (89%)
Not Reported	13 (14%)	0 (0%)
Hispanic or Latino	9 (10%)	1 (11%)
Unknown	3 (3%)	0 (0%)
Age Group		
<1 month	1 (1%)	0 (0%)
1 month to <1 year	8 (9%)	0 (0%)
1 to <2 years	3 (3%)	3 (33%)
2 to <6 years	7 (8%)	1 (11%)
6 to <12 years	6 (6%)	1 (11%)
12 to <16 years	3 (3%)	1 (11%)
18 to <45 years	22 (24%)	0 (0%)
45 to <65 years	25 (27%)	1 (11%)
65 to <75 years	13 (14%)	1 (11%)
75+ years	5 (5%)	1 (11%)
Pediatric Age Groups[1]		
Infants & Toddlers	12 (13%)	0 (0%)
Children	13 (14%)	4 (44%)
Adolescents	3 (3%)	2 (22%)
Age (years)		
N	93	9
Mean	37.9	28.4
Standard deviation	26.1	32.0
Median	41.0	12.0
Minimum	0.1	2.0
Maximum	78.0	79.0
ECOG Performance Status		
0: Normal activity	42 (45%)	5 (56%)
1: Symptoms, but ambulatory	41 (44%)	3 (33%)
2: In bed less than 50% of time	10 (11%)	1 (11%)

Visit Cut-off 30-JUL-2018

Source: CSE update, ISE, Tables 14.2.1 and 14.2.1.1.

According to the inclusion criteria, Study 15002 required age of 12 or above; however, country-specific protocol amendments were sometimes made to allow inclusion of younger patients. Amendments have thus been made to include specific, selected patients. This represents an additional source of selection bias that introduces uncertainty to the overall efficacy estimates.

The ePAS2 included paediatric and adult patients, range 0.1 – 78 years of age, median age 41 years, 53% of patients were male, and 70% were white. Most patients had a baseline ECOG score of 0 or 1 (45 and 44%, respectively). In the primary brain tumour population performance status was similar. Body weight, height, body mass index, and body surface area (BSA) all demonstrated an expected high variability in the ePAS2 due to the age distribution.

Table 44: Baseline Disease Characteristics by study and in the pooled study population

	LOXO-TRK-14001			LOXO-TRK-15002	LOXO-TRK-15003			ePAS
	TRK	Non-TRK	Total	TRK	TRK	Non-TRK	Total	TRK
N	8	62	70	63	34	9	43	73
Primary tumor type, n (%)[a]								
Lung (NSCLC)	1 (13)	10 (16)	11 (16)	6 (10)				4 (5)
Thyroid	1 (13)	2 (3)	3 (4)	9 (14)	4 (12)	0	4 (9)	6 (8)
Sarcoma				12 (19)				
Colorectal				6 (10)				6 (8)
Salivary gland	3 (38)	2 (3)	5 (7)	14 (22)				13 (18)
Biliary				2 (3)				
Primary CNS	0	1 (2)	1 (1)	3 (5)	3 (9)	5 (56)	8 (19)	
Other				11 (17)				
Bone sarcoma	0	2 (3)	2 (3)		1 (3)	1 (11)	2 (5)	2 (3)
Ewing's sarcoma					0	1 (11)	1 (2)	
Soft tissue sarcoma	1 (13)	8 (13)	9 (13)		10 (29)	1 (11)	11 (26)	18 (25)
Gastrointestinal stromal (GIST)	2 (25)	0	2 (3)		0	0	0	4 (5)
Infantile fibrosarcoma					14 (41)	0	14 (33)	10 (14)
Colon	0	8 (13)	8 (11)					
Anal	0	1 (2)	1 (1)					
Cholangiocarcinoma	0	2 (3)	2 (3)					2 (3)
Melanoma	0	2 (3)	2 (3)		1 (3)	0	1 (2)	4 (5)
Appendix	0	1 (2)	1 (1)					1 (1)
Breast	0	4 (6)	4 (6)					1 (1)
Congenital mesoblastic nephroma	0	0	0		1 (3)	0	1 (2)	1 (1)
Pancreas	0	4 (6)	4 (6)					1 (1)
Thymus	0	4 (6)	4 (6)					
Gastric	0	2 (3)	2 (3)					
Hepatic	0	2 (3)	2 (3)					
Endometrial	0	1 (2)	1 (1)					
Larynx	0	1 (2)	1 (1)					
Neuroblastoma	0	1 (2)	1 (1)		0	1 (11)	1 (2)	
Oral	0	1 (2)	1 (1)					
Ovarian	0	1 (2)	1 (1)					
Renal	0	1 (2)	1 (1)					
Cancer of unknown primary	0	1 (2)	1 (1)					
Time from diagnosis, years								
Median	6.4	3.3	3.3	2.3	0.7	1.5	0.8	2.2
Range	0.4-17.2	0.5-22.2	0.4-22.2	0.1-31.5	0.02-13.0	0.42-7.1	0.02-13.0	0.02-31.5
Disease extent at enrolment, n (%)								
Locally advanced	NR	NR	NR	NR	14 (41)	1 (11)	15 (35)	13 (18)
Metastatic	8 (100)	62 (100)	70 (100)	57 (90.5)[b]	17 (50)	2 (22)	19 (44)	60 (82)
Other[c]	NR	NR	NR	NR	3 (9)	6 (67)	9 (21)	

	LOXO-TRK-14001			LOXO-TRK-15002	LOXO-TRK-15003			ePAS
	TRK	Non-TRK	Total	TRK	TRK	Non-TRK	Total	TRK
ECOG performance status n (%)								
0	4 (50)	17 (27)	21 (30)	19 (30)				33 (45)
1	4 (50)	43 (69)	47 (67)	35 (56)				33 (45)
2	0	2 (3)	2 (3)	9 (14)				7 (10)
3	0	0	0	0				
Lansky or Karnofsky performance status n (%)								
50					1 (3)	0	1 (2)	
60					1 (3)	1 (11)	2 (5)	
70					2 (6)	2 (22)	4 (9)	
80					4 (12)	3 (33)	7 (16)	
90					7 (21)	2 (22)	9 (21)	
100					19 (56)	1 (11)	20 (47)	
Tumor Stage at diagnosis, n (%)								
I	0	7 (11)	7 (11)	4 (6)	7 (21)	1 (11)	8 (19)	7 (10)
II	3 (38)	9 (15)	12 (17)	5 (8)	10 (29)	1 (11)	11 (26)	12 (16)
III	2 (25)	14 (23)	16 (23)	16 (25)	10 (29)	1 (11)	11 (26)	22 (30)
IV	3 (38)	31 (50)	34 (49)	20 (32)	6 (18)	4 (44)	10 (23)	19 (26)
Not reported	0	1 (2)	1 (1)	18 (29)	1 (3)	2 (22)	3 (7)	13 (18)
***NTRK* gene fusion, n (%)**								
NTRK1								32 (44)
NTRK2								2 (3)
NTRK3								35 (48)
Inferred *NTRK3*								3 (4)
Result pending								1 (1)

[a] Due to differences in the way tumour histologies were recorded across the 3 studies, sarcoma, bone sarcoma, Ewing's sarcoma, soft tissue sarcoma, gastrointestinal stromal tumours, biliary, and cholangiocarcinoma have been recorded using different terms, resulting in inconsistent categorizations of the same tumour histologies across the different studies. Other tumours in Study LOXO-TRK-15002 included 1 appendix, 1 breast, 6 melanoma, 1 pancreas, 1 salivary gland non-measurable, and 1 NSCLC non-measurable

[b] 6 patients did not have metastatic disease

[c] Includes patients with primary CNS tumours and Ewing's sarcoma (left frontal parietal lesion)

Abbreviations: CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; NR = not reported; TRK = tropomyosin receptor kinase (fusion cancer)

Shaded columns are the TRK fusion-positive subgroups, pertinent to the sought indication.

Table 45: Baseline Disease Characteristics for the updated pooled primary study population (ePAS2) and primary brain tumour population (SAS3)

Status	ePAS2 (N=93)	SAS3 (N=9)	
Primary Diagnosis			
Soft tissue sarcoma	21 (23%)	0 (0%)	
Salivary gland	17 (18%)	0 (0%)	
Infantile fibrosarcoma	13 (14%)	0 (0%)	
Colon	6 (6%)	0 (0%)	
Thyroid	10 (11%)	0 (0%)	
GIST	4 (4%)	0 (0%)	
Lung	7 (8%)	0 (0%)	
Melanoma	7 (8%)	0 (0%)	
Bone sarcoma	2 (2%)	0 (0%)	
Cholangiocarcinoma	2 (2%)	0 (0%)	
Appendix	1 (1%)	0 (0%)	
Breast	1 (1%)	0 (0%)	
Congenital mesoblastic nephroma	1 (1%)	0 (0%)	
Pancreas	1 (1%)	0 (0%)	
Primary CNS	0 (0%)	9 (100%)	
Stage at Initial Diagnosis			
I	10 (11%)	1 (11%)	
II	16 (17%)	0 (0%)	
III	25 (27%)	2 (22%)	
IV	25 (27%)	2 (22%)	
Unknown/Not reported	17 (18%)	4 (44%)	
Years since Initial Diagnosis			
N	93	N	9
Mean	4.2	Mean	2.1
Standard deviation	5.7	Standard deviation	1.5
Median	2.1	Median	1.8
Minimum	0.02	Minimum	0.40
Maximum	31.5	Maximum	5.5
Disease Status at Study Enrollment			
Metastatic	77 (83%)	Metastatic	0 (0%)
Locally advanced	16 (17%)	Locally advanced	4 (44%)
		Other	5 (56%)
Documented NTRK Fusion Cancer			
Yes	93 (100%)	Yes	9 (100%)
NTRK Gene Fusion			
NTRK1	41 (44%)	Not determined	0 (0%)
NTRK2	3 (3%)	NTRK1	1 (11%)
NTRK3	45 (48%)	NTRK2	7 (78%)
Inferred NTRK3	4 (4%)	NTRK3	1 (11%)
		Inferred NTRK3	0 (0%)

NTRK Fusion Partner			KANK-NTRK2	
ETV6-NTRK3	39	(42%)	Not determined	1 (11%)
TPM3-NTRK1	17	(18%)	ETV6-NTRK3	0 (0%)
LMNA-NTRK1	10	(11%)	TPM3-NTRK1	1 (11%)
Inferred ETV6-NTRK3	4	(4%)	LMNA-NTRK1	0 (0%)
SQSTM1-NTRK1	2	(2%)	Inferred ETV6-NTRK3	0 (0%)
IRF2BP2-NTRK1	2	(2%)	SQSTM1-NTRK1	0 (0%)
SQSTM1-NTRK3	2	(2%)	IRF2BP2-NTRK1	0 (0%)
CTRC-NTRK1	1	(1%)	SQSTM1-NTRK3	0 (0%)
EML4-NTRK3	1	(1%)	BCR-NTRK2	3 (33%)
GNAQ-NTRK2	1	(1%)	AFAP1-NTRK1	1 (11%)
GON4L-NTRK1	1	(1%)	AGTPBP1-NTRK2	1 (11%)
MYO5A-NTRK3	1	(1%)	CTRC-NTRK1	0 (0%)
NFASC-NTRK1	1	(1%)	GON4L-NTRK1	0 (0%)
PDE4DIP-NTRK1	1	(1%)	KANK2-NTRK2	1 (11%)
PLEKHA6-NTRK1	1	(1%)	PDE4DIP-NTRK1	0 (0%)
PPL-NTRK1	1	(1%)	PLEKHA6-NTRK1	0 (0%)
SPECC1L-NTRK3	1	(1%)	PPL-NTRK1	0 (0%)
STRN-NTRK2	1	(1%)	SPECC1L-NTRK2	1 (11%)
TPM4-NTRK3	1	(1%)	STRN-NTRK2	0 (0%)
TPR-NTRK1	3	(3%)	TPM4-NTRK3	0 (0%)
TRAF2-NTRK2	1	(1%)	TPR-NTRK1	0 (0%)
TRIM63-NTRK1	1	(1%)	TRIM63-NTRK1	0 (0%)

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Source: CSE update, ISE, Tables 14.2.2 and 14.2.2.1, with correction of number of GIST/soft tissue carcinoma patients.

In the ePAS2, patients with 14 tumour histologies were included. Median time from diagnosis was 2.1 years for the ePAS2 and most patients had metastatic disease at enrolment (83%). Most patients had *NTRK3* fusions or *NTRK1* fusions (53% and 44%, respectively) and a baseline ECOG score of 0 or 1 (45 and 44%, respectively). In the primary brain tumour population, *NTRK2* fusions were dominating (78%) and performance status was higher.

NTRK fusion detection method

Molecular pathology reports were provided for 105 enrolled on larotrectinib studies 14001, 15002 and 15003 who fulfilled the criteria for pooling into the ePAS2 (see below). The 105 molecular pathology reports documented the results of 33 unique tests performed at 31 different labs.

Most of the tests performed were NGS-based (N = 98), while the minority were FISH-based (N = 6) and RT-PCR-based (N=1).

The NGS-based tests/methods used were reported as follows: FoundationOne (n=24), FoundationOne Heme (n=17), RNA sequencing (n=16), MSK-IMPACT (n=8), Thermo Fisher Oncomine Focus (n=8), Oncoplex (n=5), Archer FusionPlex Custom (n=6), Archer FusionPlex CTL (n=2), Solid Fusion Assay (n=2), Archer FusionPlex Solid Tumor Panel (n=1); Archer Solid Tumor FusionPlex (n=1), Archer FusionPlex (n=1), Guardant360 (n=1), and OmniSeq Comprehensive (n=1), OncoKids Cancer Panel (n=1), Oncomine Gene Panel (n=1), Oncopanel MDOPANELB (n=1), Sarcoma Fusion Panel (n=1), Trusight RNA Pan-Cancer Panel (n=1).

The FISH-based tests were: ETV6 FISH (n=4), i.e. an inferred positive NRTK fusion status, and ETV6/NTRK3 FISH (n=2).

Table 46: Prior Cancer-related Treatments by study and in the pooled study population

	LOXO-TRK-14001			LOXO-TRK-15002	LOXO-TRK-15003			ePAS
	TRK	Non-TRK	Total	TRK	TRK	Non-TRK	Total	TRK
N	8	62	70	63	34	9	43	73
Any prior therapy, n (%)	8 (100)	61 (98)	69 (99)	NR	31 (91)	8 (89)	39 (91)	72 (99)
No prior therapy, n (%)	0	1 (2)	1 (1)	NR	3 (9)	1 (11)	4 (9)	1 (1)
Prior surgery, n (%)	7 (88)	54 (87)	61 (87)	58 (92)	22 (65)	4 (44)	26 (60)	64 (88)
Prior radiotherapy, n (%)	4 (50)	36 (58)	40 (57)	43 (68)	7 (21)	7 (78)	14 (33)	36 (49)
Prior systemic therapy, n (%)	8 (100)	60 (97)	68 (97)	47 (75)	26 (76)	7 (78)	33 (77)	59 (81)
Number or prior systemic regimens								
0	0	2 (3)	2 (3)	16 (25)	8 (24)	2 (22)	10 (23)	15 (21)
1–2	3 (38)	20 (32)	23 (33)	29 (46)	21 (62)	2 (22)	23 (53)	35 (48)
≥3	4 (50)	40 (65)	44 (63)	18 (29)	5 (15)	5 (56)	10 (23)	23 (32)
Median	3.0	3.0	3.0	2.0	1.0	3.0	1.0	2.0
Range	1-10	0-11	0-11	0-9	0-4	0-9	0-9	0-10
Best response to last systemic treatment, n (%)								
Complete	1 (13)	0	1 (1)	1 (2)	1 (3)	0	1 (2)	2 (3)
Partial	0	1 (2)	1 (1)	3 (5)	0	0	0	2 (3)
Stable	2 (25)	19 (31)	21 (30)	13 (21)	16 (47)	2 (22)	18 (42)	22 (30)
Progression	2 (25)	25 (40)	27 (39)	8 (13)	5 (15)	5 (56)	10 (23)	10 (14)
Other	3 (38)	17 (27)	20 (29)	38 (60)	12 (35)	2 (14)	14 (33)	37 (51)

Other includes not evaluable, unknown, not applicable and missing
Abbreviations: ePAS = extended primary analysis set NR = not reported; TRK = tropomyosin receptor kinase (fusion cancer)

Table 47: Prior Cancer Therapy in the ePAS2 and primary brain tumours (SAS3)

Status	ePAS2 (N=93)	SAS3 (N=9)
Received Prior Cancer Treatment		
Yes	90 (97%)	9 (100%)
No	3 (3%)	0 (0%)
Prior Cancer Treatments[1]		
Surgery	78 (84%)	5 (56%)
Systemic therapy	72 (77%)	9 (100%)
Radiotherapy	45 (48%)	5 (56%)
Number of Prior Systemic Regimens		
0	21 (23%)	0 (0%)
1-2	46 (49%)	8 (89%)
3 or more	26 (28%)	1 (11%)
Number of Prior Systemic Regimens		
N	93	9
Mean	1.8	1.7
Standard deviation	1.8	1.3
Median	1.0	1.0
Minimum	0	1
Maximum	10	5
Best Response to Last Systemic Treatment		
Complete Response	3 (3%)	0 (0%)
Partial Response	3 (3%)	0 (0%)
Stable Disease	27 (29%)	5 (56%)
Progressive Disease	12 (13%)	2 (22%)
Other[2]	48 (52%)	2 (22%)

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In the ePAS2, 97% of patients had received prior surgery for their cancer, 48% had received prior radiotherapy, and 77% had received prior systemic therapy. The corresponding proportions for the primary brain tumour population were 100%, 56% and 100%. Larotrectinib was the initial systemic therapy for 23% of patients where no standard of care systemic treatment existed in the ePAS2. The median number of prior systemic regimens was 1.0, ranging from 0 to 10.

Numbers analysed

Analysis Sets for Pooled Analyses

Primary Analysis Set (PAS)

The PAS was pre-defined and based on NTRK gene fusion status, chronology of enrolment, and primary tumour histology. It included the first 55 patients – both paediatric and adult – enrolled in Study 14001, 15002, or 15003, who met the following criteria:

- Documented NTRK gene fusion as determined by local testing (see exception below)

- Non-CNS primary tumour (see rationale below)
- 1 or more measurable lesions at baseline as assessed by RECIST v1.1
- Received 1 or more doses of larotrectinib

The PAS was initially evaluated at the 17 JUL 2017 cut-off date. After this date, no patient could qualify for the PAS itself. Results from two subsequent data cut-offs with extended primary analysis sets have been presented during the evaluation, 19 February 2018 and 30 July 2018. The assessment in this report is focused on the latter.

Supplemental analysis sets (SASs)

In addition to the initial 55 patients that comprised the PAS, additional patients have been treated and evaluated with larotrectinib and are summarized in the following supplemental analysis sets (SASs):

- **SAS1** included paediatric and adult patients who met all PAS eligibility criteria but were enrolled after the 55th PAS-evaluable patient but before the subsequent data cut-offs. SAS1 utilized disease assessments performed by the Investigator as opposed to central assessment.
    - For a subset of patients in SAS1 who were enrolled before the subsequent data cut-offs, sufficient follow-up was available to permit IRC assessment of tumour responses (chance of at least 6 months of follow-up prior to the data cut-off) and these data have also been presented, this subset is referred to as SAS1-IRC.
    - The remaining patients in SAS1 did not have sufficient duration of follow-up for IRC assessment (SAS1-no IRC).
- **SAS2** included paediatric and adult patients who otherwise met PAS eligibility criteria with the exception of having a measurable lesion and were enrolled before the subsequent data cut-offs. SAS2 utilized disease assessments performed by the Investigator as opposed to central assessment. As of 30 JUL 2018, the SAS3 dataset included 7 patients with non-measurable tumours.
- **SAS3** included paediatric and adult patients with primary CNS tumours but who otherwise met PAS eligibility criteria and were enrolled before the data cut-off. SAS3 utilized disease assessments performed by the Investigator as opposed to central assessment. As of 30 JUL 2018, the SAS3 dataset included 9 patients with primary CNS tumours.

Extended Primary Analysis Sets (ePAS and ePAS2)

The ePAS (n=73) included all patients who met all PAS eligibility criteria as of 19 FEB 2018 and had central review of tumour response by the IRC. This included an additional 18 patients (SAS1-IRC) compared to the PAS (n=55).

The Extended primary analysis set 2 (ePAS2, n=93) included all patients who met all PAS eligibility criteria and had either discontinued the study or had at least 6 months follow-up by 30 JUL 2018 (thereby ensuring at least one central review of tumour response by the IRC). This included an additional 38 patients (SAS1-IRC) compared to the PAS (n=55). See Figure 23 below.

One patient was inadvertently excluded from the ePAS2 analysis set: one patient in study 15003 was a surgical complete responder. This patient discontinued the trial after his surgery on 18 JUL 2018. This patient therefore had a response assessment before 30 JUL 2018 but was excluded from ePAS2. This patient will be included in the ePAS3 analysis set.

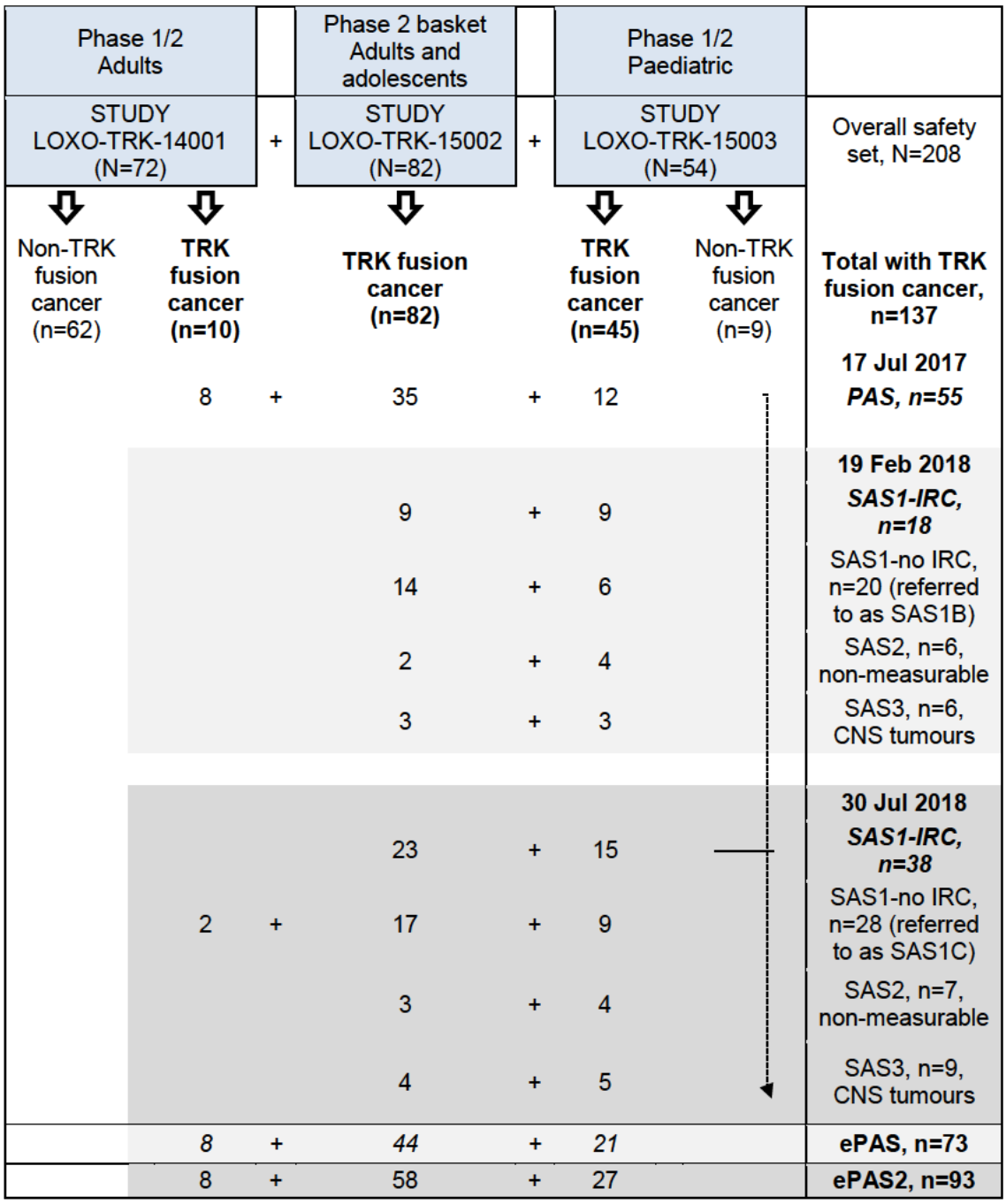
NTRK testing

Eligibility criteria for Phase 2 Study LOXO-TRK-15002 required all patients to have an NTRK gene fusion. Enrolment in Studies LOXO-TRK-14001 and LOXO-TRK-15003 was not restricted to patients with documented NTRK gene fusion. Infantile fibrosarcoma (IFS) patients (Study LOXO-TRK-15003) were considered NTRK gene fusion-positive irrespective of available NTRK gene testing based on the known incidence of the alteration in this patient population (Rubin et al. 1998; Bourgeois et al. 2000), though most had been tested prior to study enrolment with NGS, RT-PCR or ETV6 FISH analysis.

At prolonged follow-up, all patients in the primary efficacy population ePAS2 and primary brain tumour population (SAS3) did have NTRK fusion detected. In 4 IFS patients the positive NTRK fusion status was inferred from the detection of the fusion partner ETV6, however.

Exclusion of CNS tumours from pooled data sets

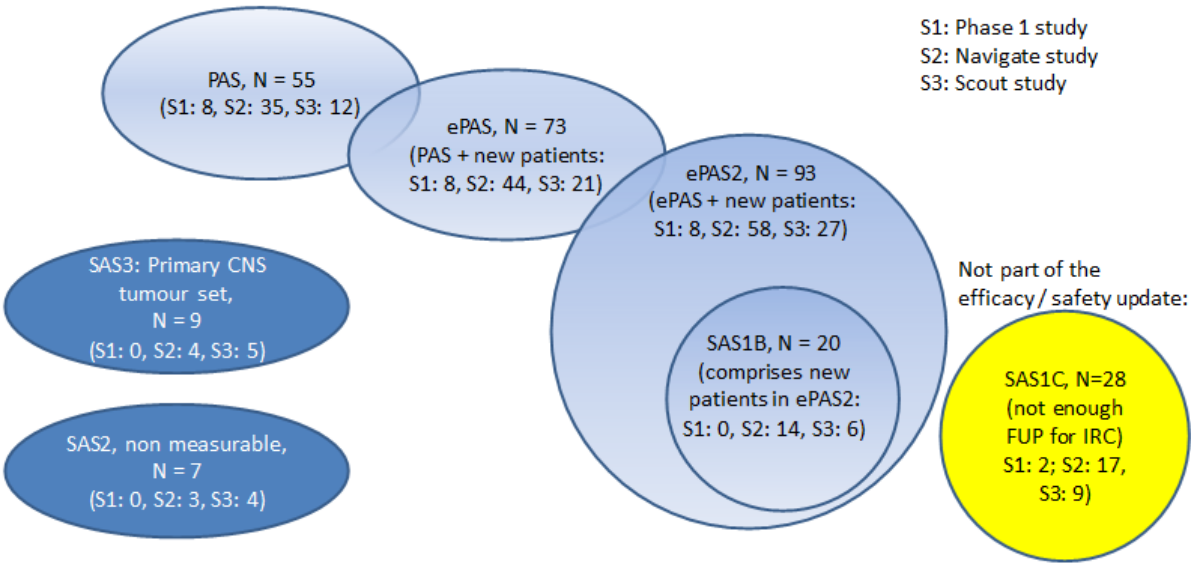
CNS tumours were excluded from the PAS because prior studies of larotrectinib in rats have indicated low penetration into CNS tissues as shown by a microdialysis study in which the unbound levels in the stratum were approximately 4% of the unbound plasma levels (LOXO-101-DMPK-035). However, CNS penetration in cancer patients taking larotrectinib may be more substantial as evidenced by 2 patients with cerebrospinal fluid samples obtained from an Ommaya reservoir and a lumbar puncture having 28% and 123% of time-matched peripheral (plasma) concentrations, respectively (LOXO-TRK-15003). The absolute concentration of larotrectinib in these two samples was 34.2 and 76.2 ng/mL (80 and 178 nM), respectively, which are approaching and exceeding the inhibitory concentration for 90% tumour inhibition (IC90) threshold for inhibition of TRK by larotrectinib. Therefore, CNS tumours constituted a standalone cohort in the Phase 2 basket study, and early stopping rules limited enrolment. This separate cohort with primary CNS tumours (cohort 7) was considered to have a lowered likelihood of response compared to the other cohorts and as such was a pre-specified exclusion from the original 55 patients to constitute the PAS.



Abbreviations: CNS = central nervous system; ePAS = Expanded primary analysis set, is a combination of PAS + SAS1-IRC as of 19 Feb 2018; ePAS2 = Expanded primary analysis set, is a combination of PAS + SAS1-IRC as of 30 Jul 2018; IRC = independent review committee; TRK = tropomyosin receptor kinase; *NTRK* = neurotrophic tyrosine kinase receptor gene; PAS = primary analysis set - included first 55 patients with documented *NTRK* gene fusion, non-CNS primary tumour with 1 or more measurable lesions at baseline as assessed by RECIST v1.1, who received 1 or more doses of larotrectinib; RECIST = Response Evaluation Criteria in Solid Tumors; SAS1 = supplemental analysis set 1- included patients meeting the same criteria as for the PAS but enrolled after the first 55 patients and not necessarily with IRC assessment; SAS1-IRC = subgroup of SAS1 with sufficient follow-up to allow IRC assessment; SAS1-no IRC = subgroup of SAS1 with insufficient follow-up to allow IRC assessment; SAS2 = supplemental analysis set 2 - included patients who met PAS eligibility criteria with the exception of having a measurable lesion; SAS3 = supplemental analysis set 3 - included patients with primary CNS tumours.

Data cut-off date: 30 July 2018

Figure 24: Enumeration of Analysis Sets



Evaluations for all analysis sets are based on clinical data with a cut-off of 30 JUL 2018.

PAS = Primary analysis set (initially used in database for 17 JUL 2017 cut-off data)

ePAS = Extended Primary analysis set (initially used in database for 19 FEB 2018 cut-off data)

ePAS2 = Extended Primary analysis set 2 (initially used in database for 30 JUL 2018 cut-off data)

SAS= Supplementary analysis set

Figure 25: Efficacy analysis sets – Data cut-off: 30 JUL 2018

In view of the post-hoc pooling of results, it is considered of outmost importance to ensure that patients selected for pooling were not "picked" based on results. The Applicant was therefore requested to present a summary of all individual patients that were excluded due to lack of IRC data (i.e., SAS1C population above). Among the 28 patients in SAS1C, 27 had treatment ongoing, range for duration of therapy was 0-4.7 months. One patient had discontinued treatment due to surgery after 4.3 months of larotrectinib treatment. This is a reassuring overall pattern as it does not indicate that patients with poorer outcomes were selectively excluded from the pooled analyses.

Outcomes and estimation

Disposition

Table 48: Patient Disposition by Study and ePAS

	LOXO-TRK-14001			LOXO-TRK-15002	LOXO-TRK-15003			ePAS
	TRK	Non-TRK	Total	TRK	TRK	Non-TRK	Total	TRK
Enrolled and treated	8	62	70	63	34	9	43	73
Treatment ongoing, n (%)	6 (75)	0	6 (9)	37 (59)	28 (82)	0	28 (65)	46 (63)
Discontinuation of treatment, n (%)	2 (25)	62 (100)	64 (91)	26 (41)	6 (18)	9 (100)	15 (35)	27 (37)
Disease progression	2 (25)	48 (77)	50 (71)	19 (30)	2 (6)	5 (56)	7 (16)	20 (27)
Clinical progression	0	0	0	0	1 (3)	1 (11)	2 (5)	-
Physician decision	0	0	0	2 (3)	0	0	0	1 (1)
Adverse event	0	5 (8)	5 (7)	2 (3)	0	1 (11)	1 (2)	1 (1)
Death	0	0	0	0	0	1 (11)	1 (2)	-
Patient decision	0	5 (8)	5 (7)	2 (3)	0	0	0	2 (3)
Non-compliance	0	2 (3)	2 (3)	0	0	0	0	-
Protocol deviation	0	0	0	1 (2)	0	0	0	-
Other	0	2 (3)	2 (3)	0	3 (9)	1 (11)	4 (9)	3 (4)

Shaded columns are the TRK fusion-positive subgroups and analysis population, pertinent to the sought indication. Abbreviation: ePAS = expanded primary analysis set; TRK = tropomyosin receptor kinase (fusion cancer)

Source: SCE Tables 3-1 and 3-6. (Data cut-off 19 Feb 2018)

Table 49: Treatment Disposition in ePAS2 and primary brain tumour population (SAS3)

Status[1]	ePAS2 (N=93)	SAS3 (N=9)
Starting Larotrectinib Dose for Adults[1]		
100 mg BID	63 (68%)	3 (33%)
150 mg BID	2 (2%)	0 (0%)
Target Larotrectinib Dose for Pediatrics[2]		
Cohort 1: 9.6-55 mg/sq meter BID	3 (3%)	0 (0%)
Cohort 2: 17.3-120 mg/sq meter BID	6 (6%)	0 (0%)
Cohort 3: 100 mg/sq meter BID	19 (20%)	6 (67%)
Progression of Disease[3,4]		
No	59 (63%)	6 (67%)
Yes	34 (37%)	3 (33%)
Treatment Continued Post-Progression		
Yes	16 (17%)	0 (0%)
Treatment Status[3]		
Continuing	53 (57%)	6 (67%)
Discontinued	40 (43%)	3 (33%)
Reason Treatment Discontinued[3,4]		
Protocol Deviation	2 (2%)	0 (0%)
Disease Progression	29 (31%)	3 (33%)
Adverse Event	2 (2%)	0 (0%)
Subject Decision	2 (2%)	0 (0%)
Other	5 (5%)	0 (0%)
Time on Treatment[3]		
Less than 3 months	13 (14%)	3 (33%)
3 to <6 months	10 (11%)	2 (22%)
6 to <9 months	14 (15%)	3 (33%)
9 to <12 months	8 (9%)	1 (11%)
12 to <15 months	13 (14%)	0 (0%)
15 to <18 months	7 (8%)	0 (0%)
18 to <21 months	7 (8%)	0 (0%)
21 to <24 months	6 (6%)	0 (0%)
24 or more months	15 (16%)	0 (0%)
Time on Treatment (months)		
N	93	9
Mean	13.5	4.9
Standard deviation	9.6	2.9
Median	12.1	4.5
Minimum	0.66	0.03
Maximum	40.7	9.2

Percentages are calculated based on the number of patients in the column heading as the denominator.
[1] Adults (18 years and older).
[2] Paediatrics (< 18 years). For Cohorts 1 and 2, the target was based on dosing calculation tables in Appendix C of Protocol 15003. For Cohort 3, the target dose was capped at 100 mg BID.
[3] Status as of 30-Jul-2018.
[4] Disease progression includes patients with clinical progression based on investigator assessment.
Source: CSE update, ISE, Table 14.1.2 and 14.1.2.1

At the time of the updated data cut-off, 30 July 2018, 57 % in the ePAS2 have treatment ongoing and 31% had experienced disease progression. The median time on treatment is 12.1 months and 52% of patients in the ePAS2 had time on treatment for 12 months' or more (Table 49).

Objective response rate

Table 50: Overall Response Rate by Study (Investigator Assessment)

	LOXO-TRK-14001		LOXO-TRK-15002	LOXO-TRK-15003	
	TRK	Non-TRK	TRK	TRK	Non-TRK
Enrolled and treated	8	62	63	34	9
CR, confirmed , n (%)	2 (25)	0	5 (8.2)	7 (21)	0
CR, pending confirmation	0	0	0	1 (3)	0
PR, confirmed	5 (63)	1 (2)	32 (52.5)	14 (41)	0
PR, pending confirmation	0	0	3 (4.9)	1(3)	0
Stable disease	1 (13)	15 (24)	9 (14.8)	10 (29)	1 (11)
Progressive disease	0	41 (66)	8 (13.1)	0	7 (78)
Not determined	0	5 (8)	1 (1.6)	0	1 (11)
Not evaluable	0	0	3 (4.9)	1 (3)	0
Number of patients evaluable	8	59 [a]	61 [b]	26 [c]	9
ORR (CR + PR) , n (%)	7 (88)	1 (2)	37 (60.7)	21 (81)	0
95% CI for ORR	47, 100	0, 9		61, 93	NC
90% CI for ORR			(51.6, NE)		
97.5% CI for ORR			(47.3, NE)		

Source: SCE, Table 3-11. (Data cut-off 19 Feb 2018)

These studies showed high response rates in patients with TRK fusion cancer, and minimal responses in patients with non-TRK fusion cancers, offering strong clinical support for the proposed mechanism of action. None of the patients without NTRK gene fusion had a best response of CR; however 1 patient, with soft tissue sarcoma with an NTRK1 gene amplification (not a fusion) and a very low volume of disease (tumours totalling 11 mm, suggesting the potential for measurement error may be large) had a transient PR of 3.8 months' duration. In addition, 16 patients without NTRK fusion had a stable disease under treatment. It should be noted that SD may simply reflect slow growing tumours.

Table 51: Response Rates in Pooled Analysis Sets by IRC and INV assessments by different data cut-offs

	ePAS (N=73)	ePAS (N=73)	ePAS2 (N=93)
Data cut-off	19 Feb 2018	30 Jul 2018*	30 Jul 2018
IRC Assessment			
Best response, n (%)			
Complete response	16 (22)	15 (21)	15 (16)
Surgical complete response	1 (1)	1 (1)	1 (1)
Partial response	38 (52)	39 (53)	51 (55)
Stable disease	10 (14)	10 (14)	14 (15)
≥16 weeks	6 (8)	6 (8)	9 (10)
Progressive disease	6 (8)	6 (8)	9 (10)
Not evaluable	2 (3)	2 (3)	3 (3)
Overall response rate [a]			
n (%)	55 (75)	55 (75)	67 (72)
95% CI	64, 85	64, 85	62, 81
Disease control rate [b]			
n (%)	61 (84)	61 (84)	76 (82)
95% CI	73, 91	73, 91	72, 89
Investigator Assessment			
Best response, n (%)			
Complete response, confirmed	13 (18)	14 (19)	16 (17)
Surgical complete response	1 (1)	1 (1)	1 (1)
Partial response, confirmed	46 (63)	45 (62)	57 (61)
Stable disease	7 (10)	7 (10)	10 (11)
≥16 weeks	3 (4)	3 (4)	5 (5)
Progressive disease	6 (8)	6 (8)	8 (9)
Not determined	0 (0)	0 (0)	1 (1)
Overall response rate			
n (%)	60 (82)	60 (82)	74 (80)
95% CI	71, 90	71, 90	70, 87
Disease control rate			
n (%)	63 (86)	63 (86)	79 (85)
95% CI	76, 93	76, 93	76, 92

Source: Efficacy Tables 14.3.1.3.2; 14.3.1.3; 14.3.1.6; 14.3.1.6.2; 14.3.5.3.2; 14.3.5.3; 14.3.5.6; 14.3.5.6.2

[a] Overall response rate is the sum of confirmed complete, surgical complete, and partial responses

[b] Disease control rate is the proportion of patients with best overall response of complete, surgical complete, partial responses, or stable disease lasting 16 weeks or more following the initiation of larotrectinib.

Abbreviations: CI = confidence interval; ePAS = expanded primary analysis set - patients meeting the same criteria as for the PAS but enrolled after the first 55 patients with IRC assessment as of 19FEB2018; ePAS2 = expanded primary analysis set - patients meeting the same criteria as for the PAS but enrolled after the first 55 patients with IRC assessment as of 30 JUL 2018; IRC = Independent Review Committee; NA = not available; PAS = primary analysis set - included first 55 patients.

Source: SCE, Table 3-13 (cut-off 19 Feb 2018); response to Day 90 question 129 (30 Jul 2018), *corrected according to source table 14.3.1.6.2 and 14.3.5.6.2, and according to response to Day 150 question 70.

Table 52: Agreement rate between IRC and investigator assessments of tumour response (ePAS2)

Status	IRC Assessment, n: Responder(Confirm CR/sCR/PR)	IRC Assessment, n: Non-Responder	Total
Investigator Assessment, n			
Responder(Confirm CR/sCR/PR)	66	8	74
Non-Responder	1	18	19
Total	67	26	93
		Agreement Rate, n(%)	
Agreement by IRC and Investigator CR/sCR/PR by Investigator, non-responder by IRC CR/sCR/PR by IRC, non-responder by investigator		84 (90.3%) 8 (8.6%) 1 (1.1%)	

Response based on assessments using RECIST (version 1.1). CR=complete response, sCR=Surgical Complete Response, PR=partial response
Source: CSE update, ISE, Table 14.3.3.9

There was 90% agreement rate (84/93) between the IRC assessment and the Investigator (INV) assessment of tumour response (confirmed CR or PR, yes vs. no).

At the time of data cut-off, 8 of 9 enrolled patients with primary CNS tumours were evaluable for response by investigator assessment.

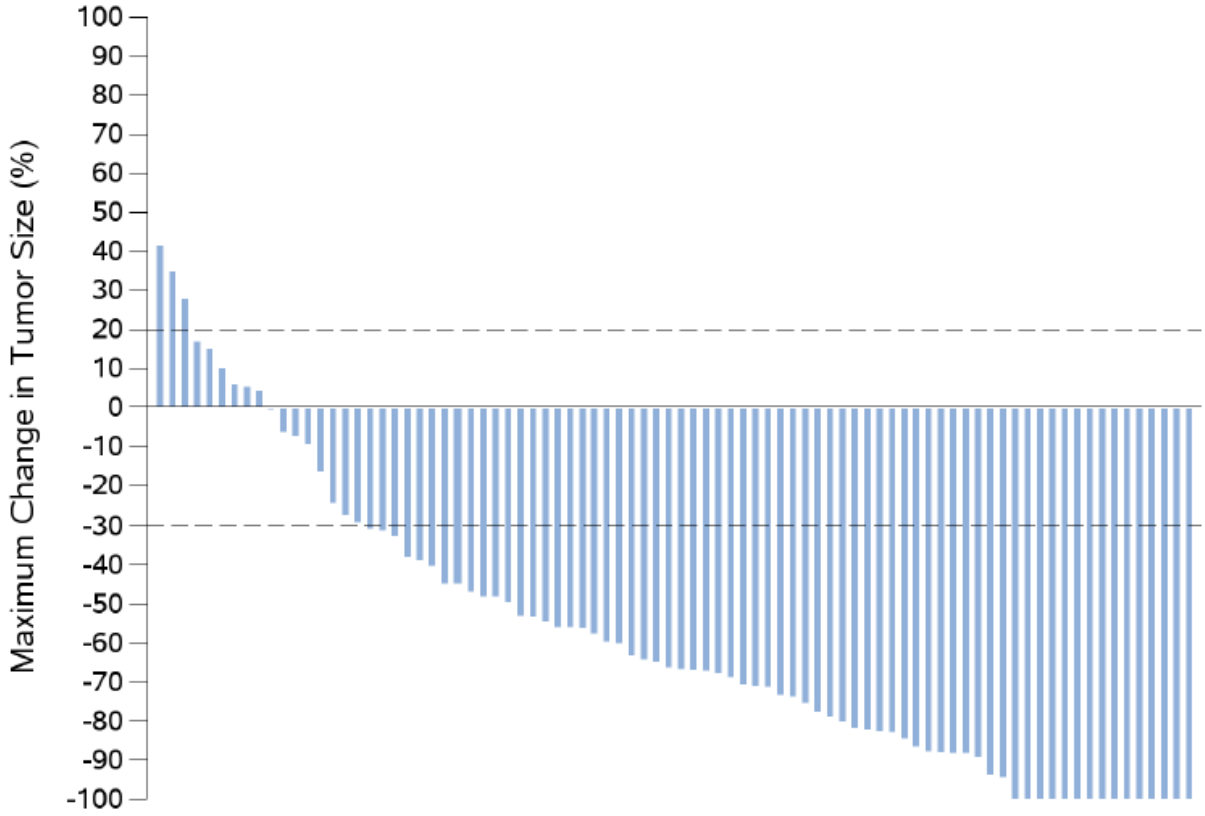
Table 53 : Best Overall Response and Overall Response Rate Based on Investigator Assessments, Primary CNS tumours (SAS3)

Status	Supplementary Analysis Set 3 (Primary CNS) (N=9)
Best Overall Response[1]	
Partial response (PR)	1 (11%)
Stable disease (SD)	7 (78%)
Not evaluable (NE)	1 (11%)
Overall Response Rate[2,3]	
Number of evaluable patients	9
Number of patients with CR + sCR + PR	1 (11%)
95% confidence interval	(0%, 48%)

Source: CSE update, ISE, Figure 14.3.6.3 Table 14.3.1.6.3

Maximum change from baseline

The Maximum change in tumour size for the updated pooled study population (ePAS2) by IRC, and the pooled primary brain tumour population (SAS3) by investigator assessments is presented below.



Abbreviations: CI = confidence interval; ePAS2 = expanded primary analysis set 2; IRC = Independent Review Committee;

Source: CSE update, ISE Figure 14.3.3.2

Figure 26: Maximum Change in Tumour Size - IRC Assessment (ePAS2)

For ePAS2, the median of the maximum percentage decrease from baseline was -66.35% (Range: -100% to 41.2%) and median absolute change was -27.54 mm (Range: -201.7 mm to 25.0 mm).

For SAS3, the median of the maximum percentage decrease from baseline was -15.4% (Range: -79.5% to 7.4%). Given that for one patient ins SAS3, RECIST criteria have been applied, the absolute change is not evaluated.

Time to response

Table 54: Time to Response Based on IRC Assessments (Subgroup of ePAS2 with Confirmed CR, sCR, or PR

Status	Extended Primary Analysis Set 2 (N=93)
Patients with Best Response of Confirmed CR, sCR, or PR[1,2]	67
Time to Response (months)[3]	
Median	1.81
25th,75th percentiles	1.71, 1.94
Minimum, Maximum	0.95, 14.55
Time to Response	
2 months or less	55 (82%)
> 2 to 4 months	7 (10%)
> 4 to 6 months	3 (4%)
> 6 to 9 months	1 (1%)
> 9 months	1 (1%)

Percentages are based on the number of patients in the analysis set or subgroup.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Best overall response classification based on radiologist and clinician assessments.
[3] Time to response is defined as the number of months elapsed between the date of the first dose of Larotrectinib and the first documentation of objective response (CR, sCR, or PR whichever occurred earlier) that was subsequently confirmed.

Source: CSE update, ISE, Table 14.3.2.3.2

Table 55: Time to Response Based on Investigator Assessments (Subgroup of ePAS2 with Confirmed CR, sCR, or PR

Status	Extended Primary Analysis Set 2 (N=93)
Patients with Best Response of Confirmed CR, sCR, or PR[1]	74
Time to Response (months)[2]	
Median	1.81
25th,75th percentiles	1.68, 1.94
Minimum, Maximum	0.89, 6.05
Time to Response	
2 months or less	60 (81%)
> 2 to 4 months	10 (14%)
> 4 to 6 months	3 (4%)
> 6 to 9 months	1 (1%)

For footnotes, see table above.

Source: CSE update, ISE, Table 14.3.2.6.2

Time to response in the ePAS2 was short and consistent at 1.8 months by IRC and INV, respectively. (IRC 25th, 75th percentiles: 1.71, 1.94 months, range 0.95, 14.55 months). A vast majority of responding patients did so at the first tumour evaluation.

The 1 patient out of 9 with Primary CNS tumours (SAS3) who had an objective response had a time to response of 1.68 months by investigator, consistent with the overall pattern for time to response.

Duration of response

Table 56: Duration of Response by Study (Investigator Assessment)

	LOXO-TRK-14001		LOXO-TRK-15002	LOXO-TRK-15003	
	TRK	Non-TRK	TRK	TRK	Non-TRK
Enrolled and treated	8	62	63	34	9
Responding patients	7	1	37	21	0
Continuing, n (%)	6 (86)	0	27 (73)	18 (86)	0
Progressed, n (%)	1 (14)	1 (100)	10 (27)	3 (14)	0
Duration of follow-up, months					
Median	26.9	NC	10.32	7.4	0
25th, 75th percentiles	18.3, 27.9		6.74, 13.83	3.8, 11.1	
Duration of response, months , n (%)					
Median	NE	3.8	NE	NE	0
Minimum, Maximum	14.7+, 33.2+		0.9+, 25.8+	1.6+, 21.3+	
≤6 months	0	1 (100)		10 (48)	
>6 months	7 (100)		81.9%	11 (52)	
>12 months	7 (100)		69.8%	4 (19)	
>18 months	6 (85.7)		55.8%	1 (5)	

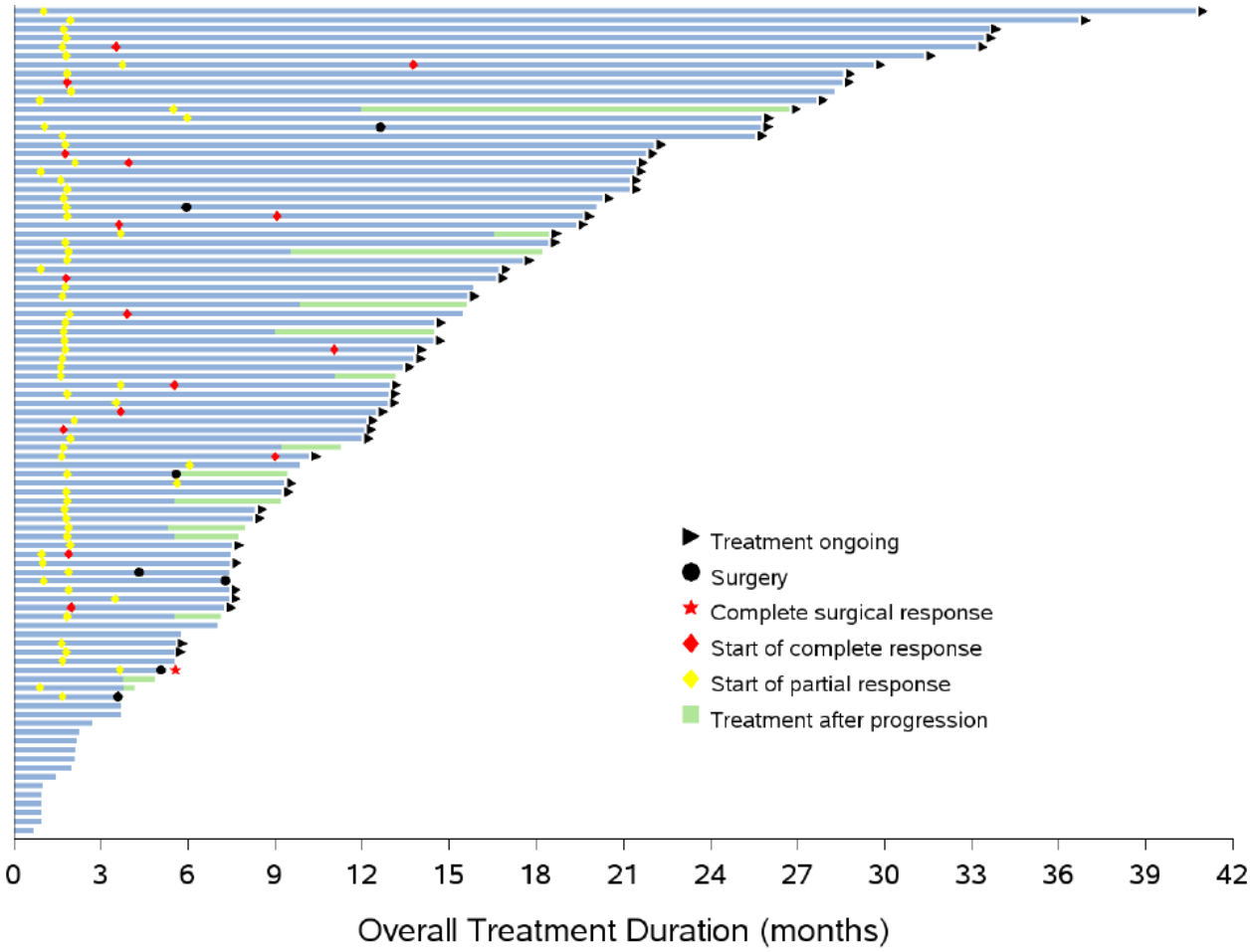
Abbreviations: + denotes censored data; NE = not estimable; TRK = tropomyosin receptor kinase (fusion cancer)
Source: SCE, Table 3-12

Table 57: Duration of Response Based on IRC Assessments (Subgroup of ePAS2 with Confirmed CR, sCR, or PR)

Status	Extended Primary Analysis Set 2 (N=93)
Duration of Follow-up (months)[4]	
Median	12.7
25th,75th percentiles	7.4, 20.3
Rate (%) of Duration of Response[4,5]	
6 months or more	88%
95% confidence interval	(80%, 96%)
12 months or more	75%
95% confidence interval	(63%, 87%)

The median duration of response was not estimable in any of the individual studies (at previous data cut-off) or in the main analysis population, ePAS2 (cut-off 30-Jul-2018), which is consistent with the high proportion of patients still in response, 73-86% in the individual studies (INV); 70% in the pooled ePAS2 population (IRC and INV). In the ePAS2, 72% of responding patients had a response that lasted 6 months or more, and 42% 12 months or more.

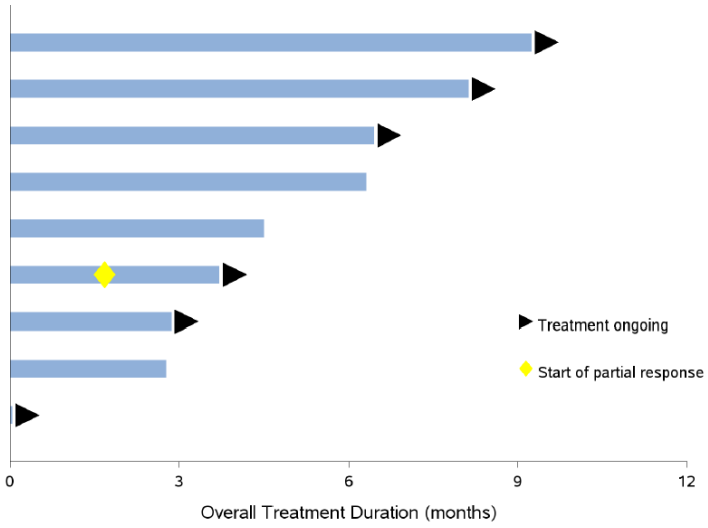
It is noted that in the previously submitted data from the ePAS (n=73) at a shorter follow-up (19 Feb 2018), 88% of responding patients had a response that lasted 6 months or more, and 72% 12 months or more (not shown). This illustrates how limited early data can overestimate the true treatment effects.



Disease assessments were performed by investigators using RECIST, version 1.1
Abbreviations: ePAS2 = expanded primary analysis set 2; RECIST = Response Evaluation Criteria in Solid Tumors

Source: CSE update, ISE, Figure 14.2.5

Figure 27: Swimmer Plot of Time to Response and Overall Treatment Duration (ePAS2)



SAS3 = Supplementary Analysis Set 3

Source: CSE update, ISE. Figure 14.2.6

Figure 28: Swimmer Plot of Time to Response and Overall Treatment Duration for Patients with Primary Brain Tumours (SAS3)

Progression-free survival

Table 58: Progression-free Survival in Pooled Analysis Sets (data cut-off 19 Feb 2018)

	PAS	ePAS
N	55	73
IRC Assessment		
Progressed or died, n (%)	22 (40)	25 (34)
Censored, n (%)	33 (60)	48 (66)
Duration of follow-up, months		
Median	15.6	13.7
25th, 75th percentiles	12.2, 22.1	8.2, 19.7
PFS, months [a]		
Median	NE	NE
95% CI	9.9, NE	11.1, NE
Minimum Maximum	0.03+, 34.2+	0.03+, 34.2+
Progression-free at 6 months, %		
Rate	75	77
95% CI	63, 87	67, 87
Progression-free at 12 months, %		
Rate	60	63
95% CI	47, 74	51, 76
Investigator Assessment		
Progressed or died, n (%)	22 (40)	25 (34)
Censored, n (%)	33 (60)	48 (66)
Duration of follow-up, months		
Median	15.6	13.7
25th, 75th percentiles	12.0, 22.1	8.7, 19.7
PFS, months [a]		
Median	28.3	28.3
95% CI	9.9. NE	17.5, NE
Minimum Maximum	0.7, 34.2+	0.7, 34.2+
Progression-free at 6 months, %		
Rate	74	76
95% CI	62, 86	66, 86
Progression-free at 12 months, %		
Rate	61	64
95% CI	48, 75	52, 76

[a] Using Kaplan-Meier method
Abbreviations: CI = confidence interval; ePAS = expanded primary analysis set; IRC = Independent Review Committee; NE = not estimable; PAS = primary analysis set; PFS = progression-free survival;

SCE, Table 3-17

At the previous data cut-off, the PFS event rate was low at 34% (25/73 patients have progressed or died), for both IRC and INV.

At the present data cut-off (30 July 2018) in the second extended primary analysis population (ePAS2), the event rate was 37% (34/93). The median PFS was 27.4 months (95% CI: 13.8, NE) by IRC and 28.3 months (95% CI: 15.2, NE) by investigator assessments. (Table 61)

Table 59: Progression-free Survival Based on IRC Assessments (ePAS2)

Status	Extended Primary Analysis Set 2 (N=93)
Progression Status[1,2,3]	
Progressed	34 (37%)
Censored	59 (63%)
Reason Censored	
Alive without documented disease progression	54 (58%)
Surgical resection of tumor without sCR	3 (3%)
No evaluable postbaseline disease assessments	2 (2%)
Duration of Progression-free Survival	
6 months or less	31 (33%)
> 6 to 12 months	26 (28%)
> 12 to 18 months	15 (16%)
> 18 to 24 months	10 (11%)
> 24 months	11 (12%)
Duration of Progression-free Survival (months)[4,5]	
Median	27.4
95% confidence interval for median	13.8, NE
Minimum, Maximum	0.03+, 39.7+

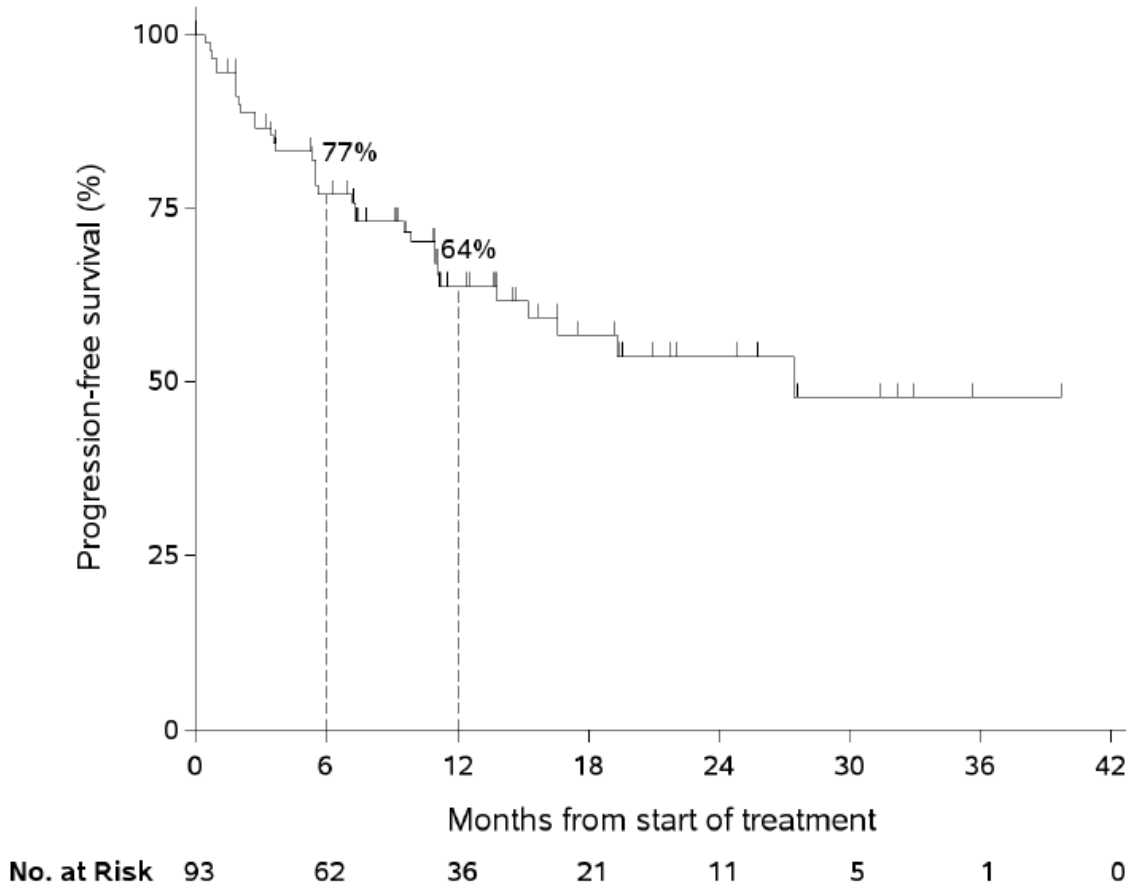
Percentages are based on the number of patients in the analysis set.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Progression status based on radiologist and clinician assessments.
[3] Status as of the patient's last disease assessment on or before 30-Jul-2018.
[4] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[5] 95% confidence interval was calculated using Greenwood's formula.

Source: CSE update, ISE, Table 14.3.6.3.2

Table 60: Progression-free Survival Based on Investigator Assessments (ePAS2)

Status	Extended Primary Analysis Set 2 (N=93)
Progression Status[1,2]	
Progressed	35 (38%)
Censored	58 (62%)
Reason Censored	
Alive without documented disease progression	53 (57%)
Surgical resection of tumor without sCR	4 (4%)
Started subsequent anticancer treatment	1 (1%)
Duration of Progression-free Survival	
6 months or less	31 (33%)
> 6 to 12 months	26 (28%)
> 12 to 18 months	14 (15%)
> 18 to 24 months	10 (11%)
> 24 months	12 (13%)
Duration of Progression-free Survival (months)[3,4]	
Median	28.3
95% confidence interval for median	15.2, NE
Minimum, Maximum	0.03+, 39.7+

Source: CSE update, ISE, Table 14.3.6.6.2



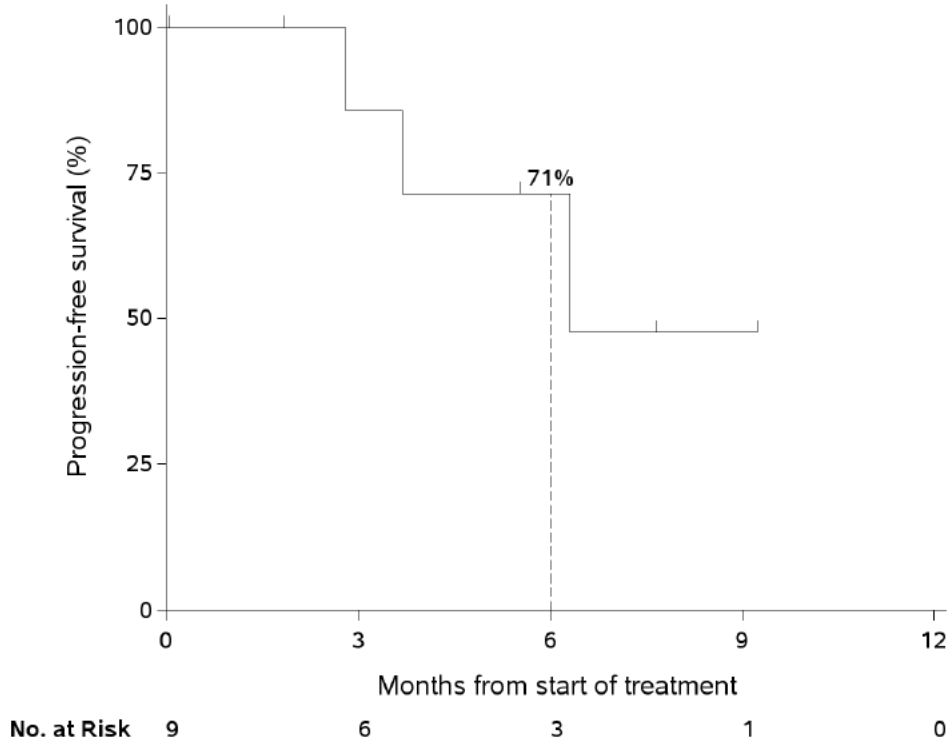
Vertical tick marks represent censored patients.

Source: CSE update, ISE, Figure 14.8.3.2

Figure 29: Kaplan-Meier Plot of Progression-free Survival - IRC Assessment (ePAS2)

PFS at 6 and 12 months in the ePAS2 (n=93) at the current data cut-off (30 Jul 2018) was 77% and 64%, respectively. This is consistent with that observed in the ePAS (n=73) at the previous data cut-off (19 Feb 2018), 77% and 63%, respectively.

PFS and OS are important for contextualisation of the ORR and DoR results and in relation to approved anticancer products normally approved based on PFS and/or OS. However, due to the pooling of many different types of primary malignancies with inherently different prognosis, the data should be interpreted with caution.



Source: CSE update, ISE, Figure 14.8.6.3

Figure 30: Kaplan-Meier Plot of Progression-free Survival Based on Investigator Assessments in patients with primary CNS tumours (SAS3)

IRC assessment were not performed in the CNS subset.

Overall survival

Table 61: Overall Survival in Pooled Analysis Sets

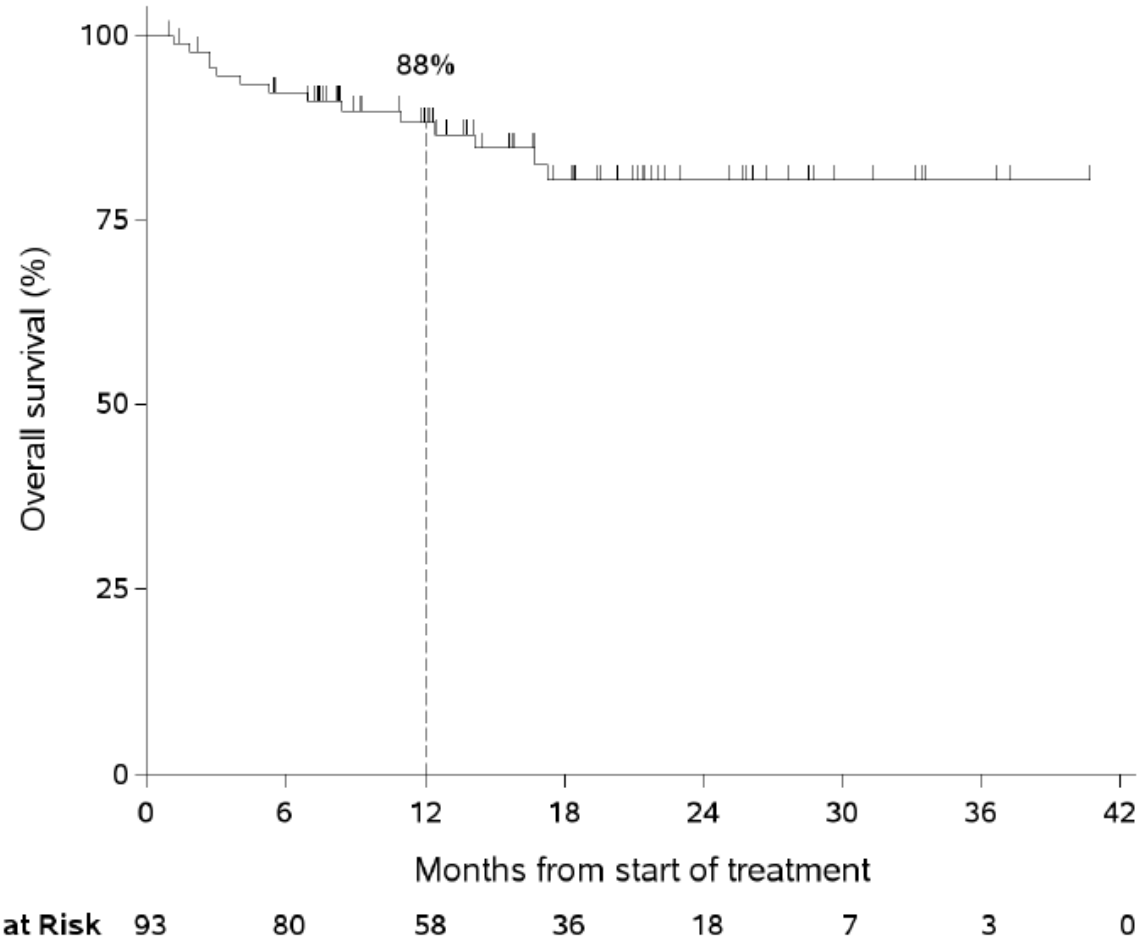
	PAS	ePAS	ePAS2	SAS3 (CNS)
Data cut-off	19 Feb 2018		30 Jul 2018	
N	55	73	93	9
Alive, n (%)	47 (85)	63 (86*)	79 (85)	9 (100)
Died, n (%)	8 (15)	10 (14)	14 (15)	
Duration of Follow-up [a]				
Median follow-up, months	16.4	14.8	16.7	4.6
25th, 75th percentiles	13.0, 23.0	8.5, 20.7	9.3, 23.0	3.7, 8.1
Duration of OS [a]				
Median survival, months	NE	NE	NE	NE
95% CI	NE, NE	NE, NE	NE, NE	NE, NE
Minimum, Maximum	1.0+, 35.2+	1.0+, 35.2+	1.0+, 40.7+	0.03+, 9.2+
Rate of Overall Survival				
Alive at 12 months, %	90	90	88	NE
95% CI	83, 98	83, 97	81, 95	NE, NE

[a] Using Kaplan-Meier method

Abbreviations: + denotes censored data, CI = confidence interval; ePAS = expanded primary analysis set; NE = not yet estimable, OS = overall survival; PAS = primary analysis set; SAS1-IRC = supplemental analysis set with IRC assessment of tumor response.

*: Percentage corrected by assessor to 86 (63/73=0.86) from the original figure 89 in the source table.

Source: SCE, Table 3-18, and CSE update, ISE, Tables 14.3.7.3.2 and 14.3.7.3.3.



OS is defined as the number of months elapsed between the date of the first dose of larotrectinib and the date of death (whatever the cause). Patients who were alive or lost to follow-up as of the data cut-off date were right-censored. The censoring date was determined from the date the patient was last known to be alive. Vertical tick marks represent the OS times for 63 patients who were alive as of the last contact.
Abbreviations: ePAS2 = expanded primary analysis set 2; OS = overall survival

Source: CSE update, ISE, Figure 14.9.3.2.

Figure 31: Kaplan-Meier Plot of Overall Survival (ePAS2)

The OS data in the ePAS2 are immature at an overall event rate of 15% (14/93 dead). Beyond approximately 28 months, less than 10 patients remain in the K-M plot. At this point, OS survival portion appears to be around 80%.

In the CNS group, all 9 patients are still alive.

Quality of life (exploratory)

In the 3rd round of assessment, the Applicant submitted patient-reported outcome (PRO) data on health-related quality of life (HRQoL), dated 22 April 2019. These are pooled data from studies 15002 (Phase 2 basket) and 15003 (Paediatric Phase 1/2). HRQoL was an exploratory objective in 15002, added during the study in a protocol amendment. In Study 15003, HRQoL was a secondary objective in the Phase 1 part (n=24). The pooled data were presented as exploratory.

In the ePAS2 population studies 15002 and 15003 contribute with 58 and 27 patients, respectively. From 15002, 48 of these 58 patients had a baseline PRO measurement and 40 had both baseline and at least one post-baseline measurement. From study 15003, 26 of the 27 ePAS2 patients had a baseline measurement and 26 had both baseline and a post-baseline measurement.

The interpretation of PROs from single-arm open-label studies is generally difficult, due to the non-blinded study design's effect on the patients' experience and the lack of comparator. In the present case, also lack of formal hypothesis testing and the missing data preclude the acceptance of any HRQoL claims in the SmPC. (It is noted that the Applicant considers that most of the patients without measurements in Study 15002 were missing due to administrative reasons.)

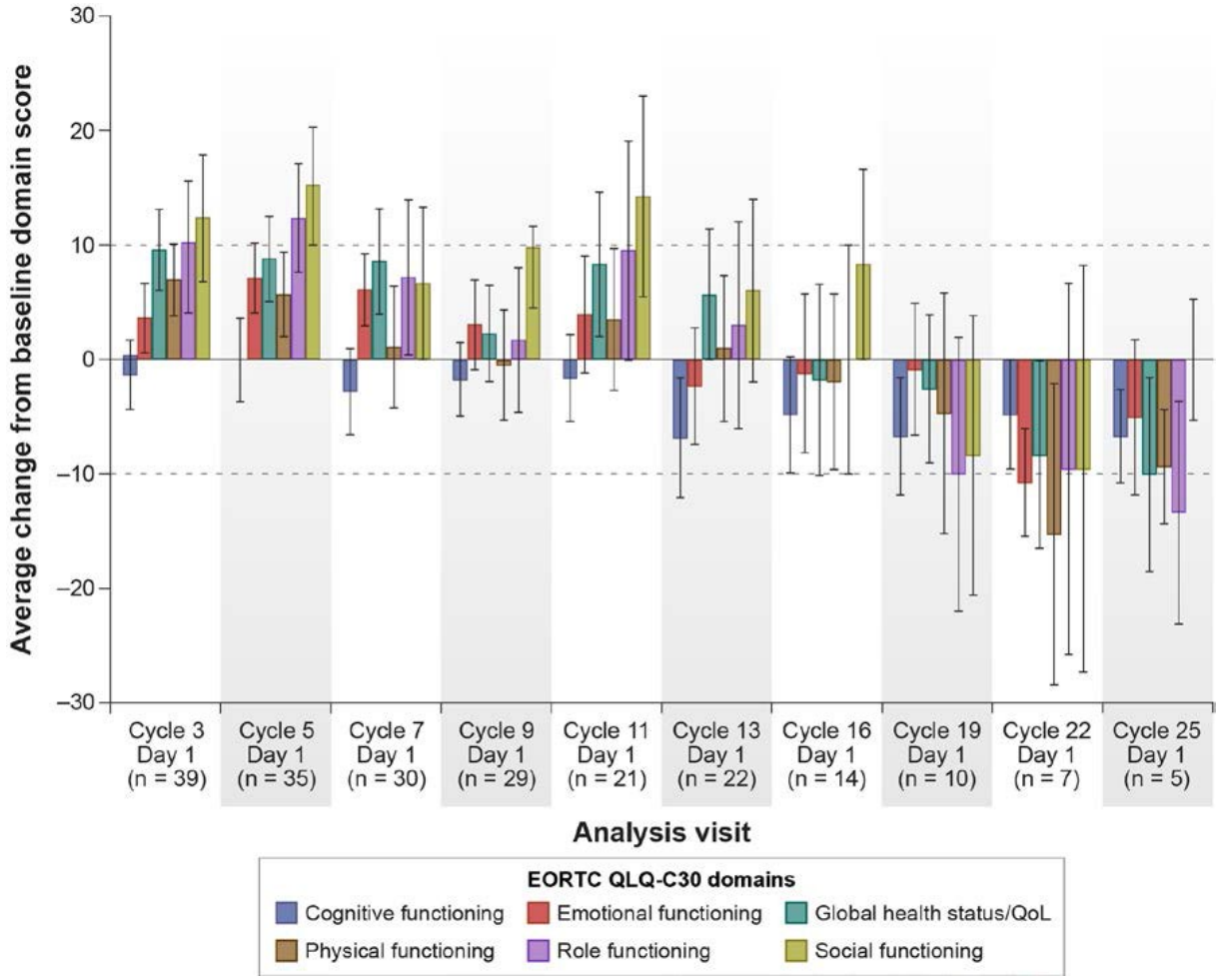
The instruments used were EORTC QLQ-C30, EQ-5D-5L, PedsQL (in several age-appropriate versions), and Wong-Baker FACES Pain Rating Scale (FACES).

For EORTC QLQ-C30, Global health status minimally important difference (MID) was defined as: a change in score of 10 points or more (Cocks et al., 2012; Osoba et al., 1998).

For EQ-5D-5L, only visual analogue scale (VAS) results were presented. VAS MID was defined as: a change in score of 10 points or more (Pickard et al., 2007)

For PedsQL, total score MID was defined as: a change in score of 4.5 points or more (Varni et al., 2007).

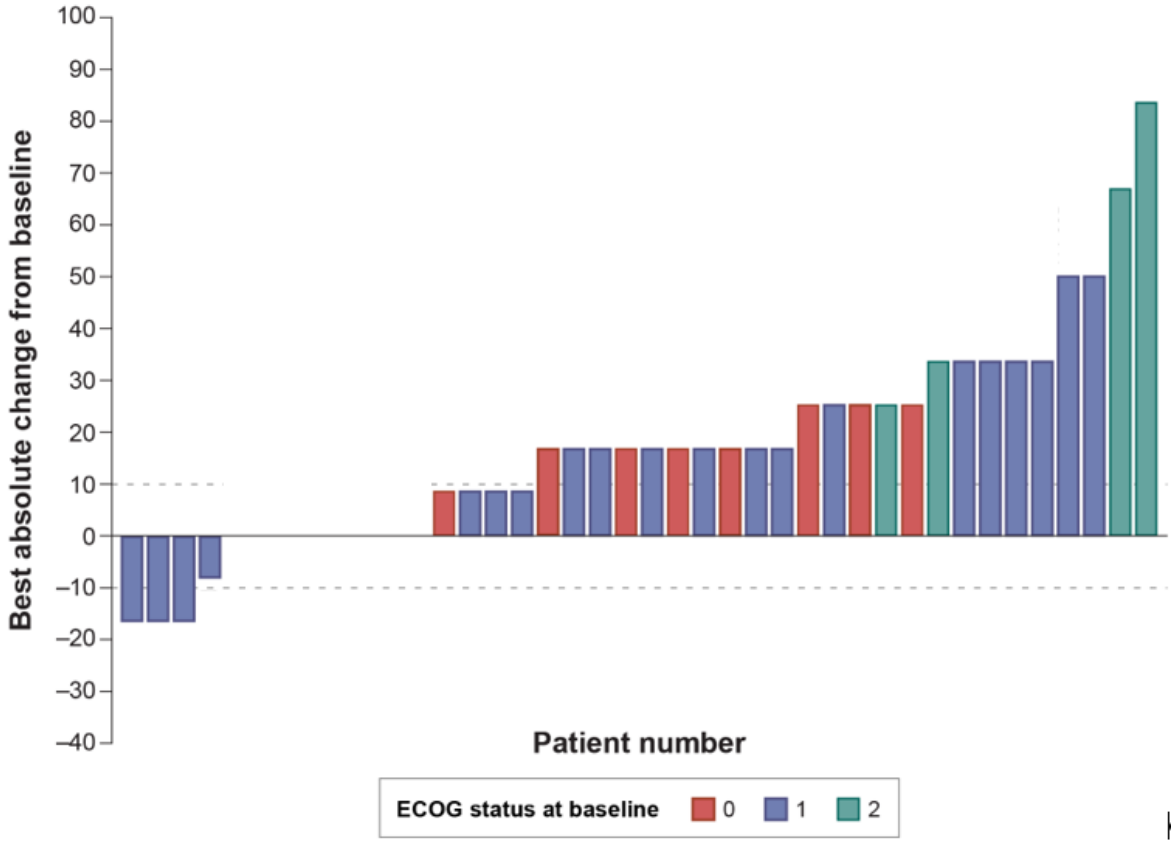
Adults



EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire– Core Module; QoL = quality of life.
Source: HRQoL report, Figure 5.
Figure 32: Average Changes From Baseline in QLQ-C30 Global Health and Functioning Scores, by Scheduled Visit

On average, postbaseline numerical increases in the Global health scores was observed for cycles 3 through 13, but it was not greater than the MID at any cycle. Postbaseline average improvement occurred in Role for cycles 3 through 13, Social for cycles 3 through 16, and Emotional for cycles 3 through 11; but

these are variables likely to be positively affected by the open-label study design. It is notable that Physical functioning shows considerably smaller average improvements. (Figure 31)



ECOG = Eastern Cooperative Oncology Group; QLQ-C30 = Cancer Quality of Life Questionnaire–Core Module.
Note: Five patients had ECOG baseline status 0, and three patients had ECOG baseline status 1.
Source: HRQoL report, Figure 4.

Figure 33: Waterfall Plot of Best Absolute Change From Baseline in QLQ-C30 Global Health Score by Baseline Eastern Cooperative Oncology Group Status

It was noted in Figure 3 (not shown) in the submitted HRQoL report that only 3 patients with progressive disease were included in the analyses of best change from baseline, possibly representing an imbalance of included patients in relation to outcome, since in the ePAS2, 8 patients had PD. (At least per 19 Feb 2018 cut-off for which individual study data have been presented, there were no PDs in study 14001, i.e. the study not included in the HRQoL analyses.)

Among the 3 patients with PD, one had no change, one had a decrease and one had >MID decrease.

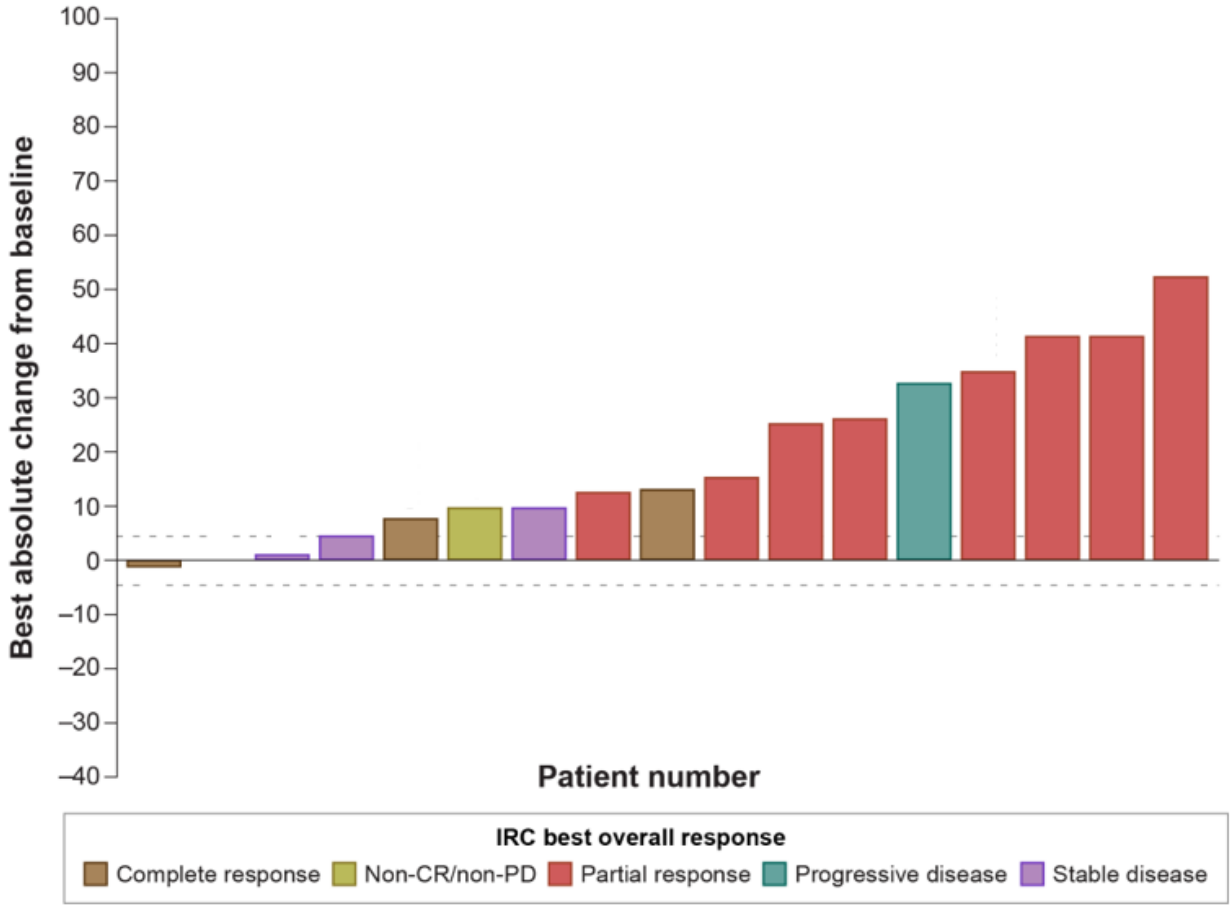
It is noted that the 4 patients with lower baseline performance status (ECOG 2) all had improvements in QLQ-C3 Global health scores over the minimal important difference (MID) threshold of 10 points difference.

The EQ-5D-5L patterns of best absolute change from baseline closely mimicked those of QLQ-C3 Global health scores shown in Figure 32. (HRQoL report, Figure 11, not shown)

Paediatric

Different instruments were used in different age groups. The 12 patients in the age group < 2 years were not interpretable due to missing data. The were 17 patients ≥2 years, 2 from 15003 and 15 from 15003.

Most patients (15 of 17) had a best postbaseline total score greater than baseline; of those, 13 had a MID improvement, defined as 4.5 points difference in score. (**Error! Reference source not found.**)



IRC = independent review committee.

Note: One patient had partial response.

Figure 34: Waterfall Plot of Best Absolute Change From Baseline in Paediatric Quality of Life Inventory Total Score, by Best Overall Response (Patients Aged 2 Years or Older)

Ancillary analyses

The pooled efficacy results for overall response rate, duration of response and time to first response, in the primary analysis population with post-hoc addition of primary CNS tumours (n=9) resulting in the pooled population (n=102), are presented in Table 54 and Table 55.

Table 62: Pooled efficacy results in solid tumours including primary CNS tumours

Efficacy parameter	Analysis in solid tumours including primary CNS tumours (n=102)[a, b]
Overall response rate (ORR) % (n) [95% CI]	67% (68) [57, 76]
Complete response (CR)	15% (15)
Surgical complete response[c]	1% (1)
Partial response (PR)	51% (52)
Time to first response (median, months) [range]	1.81 [0.95, 14.55]
Duration of response (median, months) [range] % with duration ≥ 6 months % with duration ≥ 12 months	NR [1.6+, 38.7+] 88% 75%

NR: not reached
+ denotes ongoing
[a]Independent review committee analysis by RECIST v1.1 for solid tumours except primary CNS tumours (93 patients).
[b]Investigator assessment using either RANO or RECIST v1.1 criteria for primary CNS tumours (9 patients).
[c]Paediatric patient (6 months old at enrolment) with locally advanced unresectable infantile fibrosarcoma with complete surgical response.

Table 63: 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

Analyses by subgroups are presented below.

Table 64. Overall Response Rate by Larotrectinib Starting Doses - IRC Assessment (ePAS2)

	Number of patients	CR or PR	ORR % (95% CI)
Overall	93	67	72 (62, 81)
Starting dose, n (%)			
≥18 years	65	44	68 (55, 79)
100 mg BID	63	42	67 (54, 78)
150 mg BID	2	2	100 (16, 100)
<18 years	28	23	82 (63, 94)
Cohort 1: 9.6-55.0 mg/m^2 BID	3	3	100 (29, 100)
Cohort 2: 17.3-120 mg/m^2 BID	6	6	100 (54, 100)
Cohort 3: 100 mg/m^2 BID	19	14	74 (49, 91)

Abbreviations: BID = twice daily; CI = confidence interval; CR = complete response; ePAS2 = extended primary analysis set 2; IRC – Independent Review Committee; ORR = overall response rate; PR = partial response. (Visit Cut-off 30-JUL-2018)

Based on the data presented, at the recommended starting doses for marketing authorization, the response rate was 74% for the paediatric population (100 mg/m^2 BID) and 68% for the adult population (100 mg BID). The exposures were similar in responders and non-responders, in adults and in patients <18 years of age (data not shown in this AR.)

Table 65. Overall Response Rate by Age, Sex and Race Subgroups - IRC Assessment (ePAS2)

Age Group	Number of Patients	Number of Patients with CR, sCR or PR[1]	ORR	95% CI[2]
Overall	93	67	72%	(62%, 81%)
1 month to < 2 years	12	12	100%	(74%, 100%)
2 to < 6 years	7	6	86%	(42%, 100%)
6 to < 12 years	6	2	33%	(4%, 78%)
12 to < 18 years	3	3	100%	(29%, 100%)
18 to < 65 years	47	34	72%	(57%, 84%)
65 years or older	18	10	56%	(31%, 78%)
Adults (18 years and older)	65	44	68%	(55%, 79%)
Pediatrics (< 18 years)	28	23	82%	(63%, 94%)
Male	49	39	80%	(66%, 90%)
Female	44	28	64%	(48%, 78%)
White	65	46	71%	(58%, 81%)
Other	20	17	85%	(62%, 97%)
Asian	4	3	75%	(19%, 99%)
Black or African American	4	1	25%	(1%, 81%)

Percentages are based on the number of patients in the analysis set or subgroup.
[1] Based on IRC assessments using RECIST (version 1.1). CR=complete response, PR=partial response, sCR=Surgical Complete Response.
[2] 95% confidence interval was calculated using Clopper-Pearson method.

In the ePAS2, The ORR is higher in the paediatric population, 82% (95% CI: 63, 94) compared with adults, 68% (95% CI: 55, 79). Patients aged ≥ 65 years (n=18) had a response rate of 56% (95% CI: 31, 78). Males had a moderately higher response rate (80% with 95% CI: 66, 90) than females (64% with 95% CI: 48, 79).

Table 66. Overall Response Rate by Tumour Types - IRC Assessment (ePAS2)

Tumour type	N	CR + PR	ORR % (95% CI)
Overall	93	67	72 (62, 81)
Soft tissue sarcoma	21	17	81 (58, 95)
Salivary gland (MASC and non-MASC)	17	15	88 (64, 99)
Infantile fibrosarcoma	13	12	92 (64, 100)
Colon	6	2	33 (4, 78)
Thyroid	10	7	70 (35, 93)
GIST	4	4	100 (40, 100)
Lung	7	5	71 (29, 96)
Melanoma	7	3	43 (10, 82)
Bone sarcoma	2	1	50 (1, 99)
Cholangiocarcinoma	2	0	0 (NC)
Appendix	1	0	0 (NC)
Breast (non-secretory)	1	0	0 (NC)
Congenital mesoblastic nephroma	1	1	100 (3, 100)
Pancreas	1	0	0 (NC)

Abbreviations: CI = confidence interval; CR = complete response; ePAS = extended primary analysis set; GIST = gastrointestinal stromal tumour; IRC = Independent Review Committee; MASC = mammary analogue secretory carcinoma of the salivary glands, NC = not calculated; ORR = overall response rate; PR = partial response. (Visit Cut-off 30 JUL 2018)

The response rate was also calculated in relation to the rarity of the NTRK fusion in the different tumour types, as defined by Cocco et al 2018*. The objective response rate was 87.5% in the studied tumour types in which NTRK fusion is frequent (occurring in >90% of tumours), 56.5% in patients with more common tumour types in which NTRK fusions are rare (≤25% of tumours, but in many of the tumour types here the frequency is <5%, according to Cocco et al), and 88.9% in tumour types of unclear frequency.

* Reference: Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol. 2018 Dec;15(12):731-747. doi: 10.1038/s41571-018-0113-0. Review. PubMed PMID: 30333516; PubMed Central PMCID: PMC6419506.

Table 67: Overall Response Rate by rarity of NTRK fusion and tumour types in cancers (ePAS2 + SAS3)

NTRK Fusion	Tumour Type	Number of patients	Number of responders	Overall Response Rate
Frequent NTRK	All	24	21	87.50%
	Congenital mesoblastic nephroma	1	1	100.00%
	IFS	13	12	92.31%
	Salivary gland (MASC)	10	8	80.00%
Rare NTRK	All	69	39	56.52%
	Appendix	1	0	-
	Breast (non-secretory)	1	0	-
	Cholangiocarcinoma	2	0	-
	Colon	6	2	33.33%
	GIST	4	4	100.00%
	Lung	7	5	71.43%
	Melanoma	7	3	42.86%
	Pancreas	1	0	-
	Primary CNS	9	1	11.11%
	Soft tissue sarcoma	21	17	81.00%
	Thyroid	10	7	70.00%
Unclear	All	9	8	88.89%
	Bone sarcoma	2	1	50.00%
	Salivary gland (non-MASC)	7	7	100.00%

ePAS2: Most recently updated pooled analysis population (n=93), excluding primary CNS tumours. SAS3: Primary CNS tumour subgroup, excluded from ePAS2 (n=9).

The relationship between age groups and tumour types are illustrated by Table 68.

Table 68: Tumour Type by Age Group (ePAS2 Efficacy Set, N=93)

Tumour Type	< 1 month	1 month to <1 year	1 to <2 years	2 to <6 years	6 to <12 years	12 to <18 years	18 to <45 years	45 to <65 years	65 to <75 years	75+ years
Soft Tissue Sarcoma (N=21)	0	1	1	4	3	3	6	3	0	0
Salivary Gland (N=17)	0	0	0	0	0	0	6	6	4	1
Infantile Fibrosarcoma (N=13)	0	7	1	2	2	1	0	0	0	0
Colon (N=6)	0	0	0	0	0	0	0	2	4	0
Thyroid (N=10)	0	0	0	0	1	0	2	3	2	2
GIST (N=4)	0	0	0	0	0	0	1	3	0	0
Lung (N=7)	0	0	0	0	0	0	3	2	0	2
Melanoma (N=7)	0	0	0	1	0	0	1	3	2	0
Bone sarcoma (N=2)	0	0	0	0	0	0	1	1	0	0
Cholangiocarcinoma (N=2)	0	0	0	0	0	0	1	1	0	0
Appendix (N=1)	0	0	0	0	0	0	0	0	1	0
Breast (N=1)	0	0	0	0	0	0	1	0	0	0
Congenital mesoblastic nephroma (N=1)	0	0	1	0	0	0	0	0	0	0
Pancreas (N=1)	0	0	0	0	0	0	0	1	0	0

Observed molecular changes in relation to response

Out of 93 patients in ePAS2, 85 had additional molecular characterisation, based on Next generation sequencing. In the following table, the identified genetic alterations observed in these 85 patients are summarised and categorised in relation to *OncoKb Levels of Evidence* (Table 69).

It should be noted that only the genetic changes of the highest OncoKb level of evidence for each tumour are presented in the table. Most tumours with an additional oncogenic alteration had multiple other changes of lower levels, in addition to those presented in the table.

OncoKb Levels of Evidence:

1) FDA-recognised biomarker predictive of response to an FDA-approved drug in this indication.
2) Standard care biomarker predictive of response to an FDA-approved drug in: A) this indication B) another indication, but not standard in this indication.
3) Compelling clinical evidence supports the biomarker as being predictive of response to a drug A) in this indication B) another indication, A+B) but neither biomarker or drug are standard of care.
4) Compelling biological evidence supports the biomarker as being predictive of response to a drug, but neither biomarker or drug are standard of care.
R1) Standard care biomarker predictive of resistance to an FDA-approved drug in this indication.
R2) Compelling clinical evidence supports the biomarker as being predictive of resistance to a drug, but neither biomarker or drug are standard of care.
R3) Compelling biological evidence supports the biomarker as being predictive of resistance to a drug, but neither biomarker or drug are standard of care.
(Source: https://oncokb.org/actionableGene)

Table 69: Responses in Patients with Additional Molecular Characterization (n=85) adapted from OncoKb evidence system (Chakravarti et al, 2017)

Response	Total (n)	No additional oncogenic alteration (n)	Additional oncogenic alteration (n)	OncoKB therapeutic level of evidence[a]						Preclinical evidence of oncogenic role
				1. Treatment available in tumour type	2. Treatment available in different tumour type	3. Compelling clinical evidence of predictive role	4. Biological evidence of predictive role with hypothetical therapeutic implications	R1. Standard of care biomarker associated with resistance	R2. Compelling evidence of being resistance mechanism in indication	
CR/PR	59	31 (52.5%)	28 (47.5%)	1 (1.7%) **MSI-High**[b] CRC (PR)		4 (6.8%) 2 **PIK3CA** IFS (PR) & Salivary Gland (CR) 1 **FGFR1** iSTS (CR) 1 **Flt3-IDT** salivary gland (PR)	10 (17%) 6 CDKN2A/B 2 CDKNA2 1 PTEN 1 PTEN+ CDKN2A		1 (1.7%) **Met** over expression Lung	12 (20%) Single/combinations of, e.g.: MAP2K4, MAP3K6, TP53, TERT, KDM5C, PAX5, SETD2, DNMT3A, CTNNB1, MDM4, RAF1
SD	14	4 (28.6%)	10 (71.4%)	1 (7.1%) **MSI-High**[b] CRC	1 (7.1%) **ABL1** IFS	2 (14%) 1 **PTCH1** CRC 1 **MDM2** Cholangio-sarcoma	2 (14%) 2 CDKN2A/B	1 (7.1%) **KRAS** in CRC		3 (21%) 1 TP53 1 ARID1A 1 TP53+ NOTCH1
PD	9	1 (11%)	8 (88.9%)		1 (11%) **BRAFV600E** thyroid	2 (22%) **NRASQ61** Thyroid **AKTE17K** Breast	3 (33%) 2 CDKN2A/B 1 CDKN2A/B + PTEN+NF1		1 (11%) "Long list of genes with amplification and deletion"	1 (11%) SMARCA4
NE	3	1 (33%)	2 (66%)			1 (33%) 1 **PTCH1+ PTEN** (Lev. 4)				1 (33%) ARID2
TOTAL	85	37	48	2	2	9	15	1	2	17
ORR		**31/37=84%**	**28/48=58.3%**							

[a] OncoKb Levels of Evidence, see text above, *Source: https://oncokb.org/actionableGenes.*
[b] In the EU, no drug is approved for use in MSI high tumours at present. Such indication is approved by the US FDA.
Please note that only the genetic changes of the highest OncoKb level of evidence for each tumour are presented in the table. Most tumours with an additional

molecular alteration had multiple other changes of a lower OncoKb level, in addition to those presented in the table.

Among the 85 patients with wider molecular characterisation 48 (56%) had additional oncogenic alterations, while 37 (44%) had no other oncogenic alteration detected. Three (3.5%) were not evaluable for tumour response. In relation to response outcomes, it is noted in Table 69 that among 59 patients with objective response (CR or PR), 31 (53%) had no additional oncogenic alteration, while 28 (47%) did have an additional oncogenic alteration, i.e. similar to the overall proportion. The proportions of patients with additional oncogenic alterations were higher, however, in 14 patients with SD (10 patients, 71%) and 9 patients PD (8 patients, 89%) as best response.

Correspondingly, a difference is noted in the overall response rate between patients with oncogenic alterations (28 CR/PR out of 48 patients: ORR= 58%) and patients without (31 CR/PR out of 37 patients: ORR= 84%). However, the response rate is considered high for both groups of patients. No association could be identified with either a specific oncogenic driver or tumour type and the clinical response seen in patients. Specifically, among the 9 patients with PD as best response, no trend of a particular other oncogenic driver could be seen.

No patient had a concomitant genetic alteration for which another targeted drug is approved for the concerned tumour type in the EU (MSI high noted in the table is approved in the US, but not EU). MSI high was found in one patient with PR and one with SD, respectively. There was one patient with papillary thyroid cancer with a BRAFV600E mutation that was treated with larotrectinib. While BRAF-targeted therapies exist, there is currently no BRAF inhibitor approved for the treatment of papillary thyroid cancer.

It is furthermore noted in source tables (not shown) that among, for example, 20 patients who had additional molecular characterisation and achieved either CR (PFS range 11 to >33 months) or PR with PFS >24 months, known oncogenic alterations were present in 11 patients, involving FGFR1, PIK3CA and FLT3 (OncoKb level 3), CDKN2A/B (OncoKb level 4), and MAP2K4, MAP3K6, TP53, TERT, KDM5C, and NF1. Such alterations do thus not seem to preclude relevant clinical benefit from larotrectinib treatment.

Acquired resistance

Secondary (acquired) resistance mechanisms to larotrectinib treatment were investigated.

Acquired resistance mutations after progression on TRK inhibitors have been observed. Larotrectinib had minimal activity in cell lines with point mutations in the TRKA kinase domain, including the clinically identified acquired resistance mutation, G595R. Point mutations in the TRKC kinase domain with clinically identified acquired resistance to larotrectinib include G623R, G696A, and F617L.

Out of 55 patients in the PAS population, 17 had PD after an initial response; from 10 of these the Sponsor obtained post-progression biopsies. In 8/10 patients NTRK resistance mutations were detected and in the remaining 2 patients, BRAFV600E mutations were identified. However, based on additional information, one of these patients also had a NTRK resistance mutation, and the other had very low levels of the BRAFV600E mutation (<1% allelic fraction) in circulating tumour DNA, hampering the interpretation of the role of the BRAF mutation.

Clinical trials are ongoing with second-generation TRK inhibitors (such as LOXO-195) that have been shown to be able to overcome the acquired NTRK mutations.

Secondary NTRK mutations altering the kinase domain of TRK appear to be a major acquired resistance mechanism to larotrectinib. Information on the NTRK mutations causing resistance is presented in the SmPC. Such mutations are detected by commonly used NGS techniques. Furthermore, the Applicant has committed to continue the investigation of resistance mechanisms in post-progression biopsies as part of the required post-authorisation studies.

Table 70. Duration of Response by Tumour Types - IRC Assessment (ePAS2, Subgroup of Patients with Confirmed CR, sCR, or PR)

Primary Diagnosis	Number of Patients with CR/sCR/PR[1,2]	Number (%) of Patients without Subsequent Progression/Death	Median (Range) Duration of Response in Months[3]	Rate (%) Duration of Response at 6, 12 Months[3]
Overall	67	50 (75)	NE (1.58+, 38.70+)	88%, 75%
Soft tissue sarcoma	17	13 (76)	25.63 (1.87+, 38.70+)	86%, 78%
Salivary gland	15	13 (87)	NE (3.71+, 33.68+)	100%, 91%
IFS	12	9 (75)	NE (1.58+, 17.28+)	80%, 60%
Thyroid	7	5 (71)	NE (3.71, 29.80+)	86%, 86%
Lung	5	4 (80)	NE (7.39+, 25.79+)	100%, 75%
GIST	4	2 (50)	17.35 (7.39+, 20.01+)	100%, 67%
Melanoma	3	2 (67)	NE (1.87+, 23.20+)	50%, 50%
Colon	2	1 (50)	NE (5.55, 9.17+)	50%, NR
Bone sarcoma	1	0 (0)	9.49 (9.49, 9.49)	100%, 0%
Congenital mesoblastic nephroma	1	1 (100)	NE (9.79+, 9.79+)	100%, NR

Percentages are based on the number of patients in the analysis set or subgroup.
[1] Based on IRC assessments using RECIST (version 1.1). CR=complete response, PR=partial response, sCR=Surgical Complete Response.
[2] Best overall response classification based on radiologist and clinician assessments.
[3] Estimated using Kaplan-Meier method. NE=Not estimable. NR=Not reached. + indicates censored observation. (Visit Cut-off 30-JUL-2018)

Source: Response to Day 150 Question 76, table 1075

Table 71. Overall Response Rate by NTRK Gene Fusion and by Major NTRK Isoforms – IRC Assessment (ePAS2)

Tumour type	N	CR + PR	ORR % (95% CI)
Overall	93	67	72 (62, 81)
Fusion			
NTRK3	49	40	82 (68, 91)
NTRK1	41	26	63 (47, 78)
NTRK2	3	1	33 (1, 91)
Isoform			
ETV6-NTRK3	43	36	84 (69, 93)
TPM3-NTRK1	17	12	71 (44, 90)
LMNA-NTRK1	10	6	60 (26, 88)

NTRK gene isoforms reported by ≥4 patients are shown in the table
Abbreviations: CI = confidence interval; CR = complete response; ePAS = extended primary analysis set; IRC = Independent Review Committee; *NTRK* = neurotrophic tyrosine kinase receptor gene; ORR = overall response rate; PR = partial response.

The ORRs per NTRK fusion type was 82% (95% CI: 68, 91%) for *NTRK3* (n=49), 63% (95% CI: 47, 78%) for *NTRK1* (n=41), and 33% (95% CI: 1, 91%) for *NTRK2* (n=3). Note the wide confidence intervals.

Table 72. Overall Response Rate by NTRK Fusion Isoform Based on IRC Assessment (ePAS2)

NTRK Fusion Isoform	Number of Patients	Number of Patients with CR, sCR or PR[1]	ORR	95% CI[2]
Overall	93	67	72%	(62%, 81%)
ETV6-NTRK3	43	36	84%	(69%, 93%)
TPM3-NTRK1	17	12	71%	(44%, 90%)
LMNA-NTRK1	10	6	60%	(26%, 88%)
TPR-NTRK1	3	1	33%	(1%, 91%)
IRF2BP2-NTRK1	2	2	100%	(16%, 100%)
SQSTM1-NTRK1	2	2	100%	(16%, 100%)
SQSTM1-NTRK3	2	1	50%	(1%, 99%)
CTRC-NTRK1	1	0	0%	NC
EML4-NTRK3	1	0	0%	NC
GNAQ-NTRK2	1	0	0%	NC
GON4L-NTRK1	1	0	0%	NC
MYO5A-NTRK3	1	1	100%	(3%, 100%)
NFASC-NTRK1	1	0	0%	NC
PDE4DIP-NTRK1	1	1	100%	(3%, 100%)
PLEKHA6-NTRK1	1	0	0%	NC
PPL-NTRK1	1	1	100%	(3%, 100%)
SPECC1L-NTRK3	1	1	100%	(3%, 100%)
STRN-NTRK2	1	1	100%	(3%, 100%)
TPM4-NTRK3	1	1	100%	(3%, 100%)
TRAF2-NTRK2	1	0	0%	NC
TRIM63-NTRK1	1	1	100%	(3%, 100%)

Percentages are based on the number of patients in the primary analysis set or subgroup.
[1] Based on IRC assessments using RECIST (version 1.1). CR=complete response, PR=partial response.
[2] 95% confidence interval was calculated using Clopper-Pearson method. NC=Not calculated.

Source: CSE update, ISE, Table 14.3.12.7.5.

Table 73. Overall Response Rate by Cancers Pathognomonic for NTRK Fusions Based on IRC Assessment (ePAS2)

Cancers Pathognomonic for NTRK Fusions	Number of Patients	Number of Patients with CR, sCR or PR[1]	ORR	95% CI[2]
Overall	24	21	88%	(68%, 97%)
Infantile fibrosarcoma	13	12	92%	(64%, 100%)
Salivary gland (MASC)	10	8	80%	(44%, 97%)
Congenital mesoblastic nephroma	1	1	100%	(3%, 100%)

For footnotes, see table above.

Response rate by detection method

Out of 105 patients fulfilling the pooling criteria, 98 had their positive *NTRK* fusion status identified by Next generation sequencing (NGS), considered by the Applicant to be the detection method of choice.

One patient had a PCR-based NTRK fusion status (IFS). This patient had an objective response.

Six patients had their positive *NTRK* fusion status identified by FISH.

In 2 patients, a dual gene FISH assay was used that detected *ETV6* and *NTRK3,* while the detection of an in frame NTRK fusion is only indirect. These 2 patients, with MASC and salivary gland carcinoma, respectively, both achieved complete remission.

In 4 patients a break-apart FISH assay was used in which the probes detected a gene disruption of *ETV6* and the presence of an *NTRK* fusion was thus indirectly inferred. These patients were diagnosed with infantile fibrosarcoma (IFS), an indication which is defined by a high prevalence of ETV6-NTRK3 fusions

(Sheng et al. 2001). The ORR for these patients was 100% (3 PR, 1 surgical CR), which confirms that the gene fusion very likely was expressed in these cases.

It should be noted that ETV6 has been shown to fuse with non-NRTK genes in malignant cells (Ito Y et al., Am J Surg Pathol, 2015). Furthermore, recent data show an increased spectrum of gene fusions associated with infantile fibrosarcoma and congenital mesoblastic nephroma that do not involve ETV6 (Church AJ et al., Mol Pathol, 2018).

Table 74: Overall Response Rate by Best Overall Response to Most Recent Systemic Regimen Based on IRC Assessment (ePAS2)

Best Overall Response to Most Recent Systemic Regimen	Number of Patients	Number of Patients with CR, sCR or PR[1]	ORR	95% CI[2]
Overall	93	67	72%	(62%, 81%)
Other[3]	48	35	73%	(58%, 85%)
Stable Disease	27	21	78%	(58%, 91%)
Progressive Disease	12	8	67%	(35%, 90%)
Complete Response	3	2	67%	(9%, 99%)
Partial Response	3	1	33%	(1%, 91%)

Clinical studies in special populations

Table 75: Clinical studies in elderly populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Efficacy and safety trials			
Controlled Trials	n.a.	n.a.	n.a.
Non Controlled trials			
LOXO-TRK-14001 N=72 (100%)	17 (24%)	4 (6%)	0
LOXO-TRK-15002 N=82 (100%)	19 (23%)	7 (9%)	0
LOXO-TRK-15003 N=54 (100%)	0	0	0
Total N=208 (100%)	36 (17%)	11 (5%)	0

Two of the three trials forming the basis for this application included paediatric patients. Study 15003 performed in the paediatric population, and included patients in ages 0.1-19.9 years (range for both the NTRK fusion-positive subgroup and the total study population). Furthermore, Study 15002 included patients aged 12 and older, although one patient aged 6 years appears to have been included (Table 42).

Supportive study(ies)

Supportive data of relevance to the histology-independent indication is summarised below.

29 patients had been treated in single patient protocols in the US or under compassionate use outside the US. Formal data collection was not mandated. Examples of partial responses in patients with breast cancer (including one triple-negative) and recurrent glioblastoma multiforme, as well as complete responses in patients with IFS (surgical CRs) and STS were reported, however.

Addressing the histology-independent indication, the Applicant has reported preliminary, investigator-assessed, outcomes of two patients, with non-secretory breast cancer and on the first patient with prostate cancer, who entered the pooled study population after the data cut-off for the ePAS2. Both have larotrectinib treatment ongoing.

The patient with non-secretory breast cancer had metastatic disease in liver, adrenal gland, lymph nodes and brain. The investigator reported a partial response after cycle 2 with a tumour reduction of 48%; PR was confirmed at the subsequent cycle 4 assessment, followed by an unconfirmed complete response on cycle 8.

The patient with prostate cancer had metastatic disease in bone and lymph nodes. The investigator reported stable disease at the first tumour assessment after cycle 2, and an unconfirmed partial response at cycle 4 with tumour reduction of 34%.

Updated investigator-based data on intracranial activity of larotrectinib, reported at ASCO 2019, was also submitted.

Based on the 30 July 2018 ePAS2 data cut-off, 6 patients were identified with non-primary CNS tumours with brain metastases. They had thyroid cancer (1 papillary, 1 follicular) and NSCLC, and a median age of 65 years (range 25-76). 5/6 had prior systemic therapy and 2 patients had prior radiotherapy to the brain > 1 year before larotrectinib, and 1 of these also had CNS surgery > 1 year prior. One patient had not yet had a tumour assessment. Among 5 evaluable patients 3 had PR (2 thyroid, 1 lung) and 2 had SD (lung); overall ORR was 60% (95% CI: 15-95). Partial responses occurred at cycle 2 (1 lung), and cycle 4 (2 thyroid).

Based on a new data cut-off, 19 February 2019, 18 patients with primary CNS tumours were identified in the 3 pivotal studies (n=109). Histologies included 6 glioblastoma, 4 glioma, 3 glioneuronal, 3 not otherwise specified, and 2 astrocytoma. Median age was 10 years (range 1-79); 14 patients were paediatric and 4 adults. 15 (83%) had prior systemic therapy, 13 (72%) had prior local surgery or radiotherapy. Among 14 evaluable patients, 2 CR, 3 PR, and 9 SD were noted per investigator-assessment. ORR was 36% (95% CI: 13-65). 4 of the responses occurred before/at cycle 2, the remaining 1 PR at the cycle 4 assessment. All responses were seen in paediatric patients (11 evaluable).

2.5.2.1. Comparison with available therapies

Article 14-a of Regulation (EC) No 726/2004 provides that Conditional marketing authorisations (CMA) are granted to meet 'unmet medical needs' of patients. 'Unmet medical needs' means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected.

To justify that a major therapeutic advantage of Vitrakvi (larotrectinib) over available treatment options, the following comparison with available literature data was provided.

Note that the higher ORRs compared with conventional chemotherapies that are generally observed for targeted agents such as ALK, EGFR and BRAF inhibitors (for which patients are selected based on the presence of the target molecule in the tumour) are not relevant for a larotrectinib comparison unless patients would have both drivers, which apparently is very unlikely/rare. Therefore, comparison should only be made against the molecularly unselected therapies. In comparison with these, and considering that larotrectinib is given in a later line where lower efficacy is generally expected, the larotrectinib ORR and PFS range seem overall favourable or at least comparable, although the data are far from comprehensive.

Table 76. Comparison of Larotrectinib with Available Systemic Treatment for Cancer (by Tumour Type)

Tumour Site	Available Treatments (range of data across available publications)					Larotrectinib (ePAS2)		
	Treatment line	N	CR+PR (%)	PFS (months)	OS (months)	N	CR+PR (%)	PFS range (months)
Soft tissue sarcoma	First[a]	30-228	8 - 26	3.0-7.4	8-26.5	21	81	0.46 to 39.69+
	Second [b]	16-345	1.6 - 45.8	1.5-6.6	11.5-19.5			
Salivary gland carcinoma	First/ second [c]	8-45	0 - 60	2.1-64	4-35	17	88	0.72 to 35.58+
Infantile fibrosarcoma	Vincristine- dactinomycin[d]	56	71	NR	NR	13	92	3.22+ to 20.9+
Colorectal	First [e]	122-701	18 – 65.1	4.2 – 12.1	12 – 31.0	6	33	1.48+ to 11.2+
	Second [f]	109-650	3.3 - 35	2.6 – 14.2	10.0-21.5			
	Further [g]	111-534	0.4 – 22.9	1.5 – 4.1	5.0 – 10.4			
Thyroid cancer	Any [h]	2 - 231	0 – 64.8	1.6 - 61	3.0 - 35	10	70	0.92 to 31.38+
Gastrointestinal Stromal tumour	First (imatinib)	147-473	51.0 – 68.1	20.4 – 24.0	46.8 - 57	4	100	10.87+ to 21.75+
	Second (sunitib)	61- 207	7 – 13.0	5.5 – 7.8	24.6			
	Further (regorafenib)	34-133	4.5 – 11.8	4.8 – 10.0	NR			
Lung cancer (EGFR and ALK negative)	First [i]	88 - 290	9.9 – 22.7	3.1 – 5.5	6.4 – 14.3	7	71	1.81+ to 27.6+
	Second [j]	104 - 659	3 – 22.9	1.9 – 10.6	4.6 – 12.7			
Lung cancer (EGFR mutated)	Any [k]	75 - 723	23 – 72.5	2.2 – 16.0	6.9 – 245			
Lung cancer (ALK mutated)	Any [l]	83 - 189	20 – 82.9	1.6 – 25.7	16.7 – 26.0			
Malignant melanoma	First [m]	47 - 655	11 - 61	2.2 – 11.5	9.1 – 37.6	7	43	0.03+ to 24.84+
	Second [n]	133 - 272	10.6 – 31.7	2.86 – 4.7	10.1			
Malignant melanoma (BRAF mutated)	First [o]	63 - 338	5 - 69	1.5 – 12.3	10.3 – 25.1			
	Second [p]	23 - 132	10 - 57	3.0 – 6.8	10.0 – 15.9			

Data cut-off 18Feb2018
+ patient still ongoing
The different treatment options used for each histology type are shown in the following footnotes.
a Doxorubicin, Doxorubicin+Olaratumab, Doxorubicin+Ifosfamide, Gemcitabine+docetaxel, Gemcitabine, Paclitaxel. Paclitaxel both first and second line.
b Trabectedin, Dacarbazine, Pazopanib, Eribulin, Paclitaxel + bevacizumab, Paclitaxel.
c Paclitaxel, Gemcitabine, Epirubicin + Plat + 5FU, Cisplatin + vinorelbine first line, Cisplatin + vinorelbine second line, Mitoxantrone+Cisplatin, Plat + Gemcitabine, Cyclophosphamide, doxorubicin + cisplatin, Cisplatin + Imatinib, Cetuximab + Cis + 5FU
Pembrolizumab, Sorafenib, Dovitinib, Imatinib, Lapatinib, Sunitinib, Everolimus, Nelfinavir, Bortezomib, Gefitinib
d Limited data available from case series only
e IFL, fluorouracil, leucovorin, Irinotecan, FOLFOX, Oxiplatin + irinotecan, FOLFIRI, XELOX, FUOX, FOLFOXFIRI, IFL + bevacizumab, FOLFIRI + bevacizumab, FOLFOXIRI + bevacizumab, FOLFOX/XELOX + bevacizumab, FOLFOX/XELOX, FOLFIRI + cetuximab, FOLFOX + panitumumab
f Capecitabine + irinotecan, FOLFIRI, FOLFOX, Fluoropyrimidines, Fluoropyrimidine+ irinotecan, Fluoropyrimidine + oxaliplatin, Oxaliplatin + bevacizumab, Bevacizumab, oxaliplatin + fluoropyrimidine
g Cetuximab, Cetuximab + irinotecan, Panitumumab, Regorafenib + best supportive care, Placebo + best supportive care, Trifluridine/tipiracil + best supportive care
h Doxorubicin, Doxorubicin + cisplatin, Sorafenib, Lenvatinib, Doxorubicin + cisplatin + bleomycin, Paclitaxel, Docetaxel, Axitinib, Lenvatinib, Dabrafenib + trametinib, Everolimus, Imatinib, Lenvatinib, Pazopanib, Sorafenib, Vandetanib, Vemurafenib, Fosbretabulin + paclitaxel + carboplatin, Paclitaxel + Efatutazone, Efatutazone
i Cisplatin +paclitaxel, Cisplatin + gemcitabine, Cisplatin + docetaxel, Carboplatin and paclitaxel, Vinorelbine, gemcitabine, Vinorelbine + gemcitabine, Docetaxel
j Pemetrexed, Docetaxel, Best supportive care, Nivolumab, Pembrolizumab, Ramucirumab + docetaxel, Nintedanib + docetaxel, Afatinib, Erlotinib
k Gefitinib, Carboplatin + paclitaxel, Docetaxel, Erlotinib, Cisplatin + docetaxel, Erlotinib and bevacizumab, Afatinib, Gefitinib, Cisplatin + Pemetrexed, Osimertinib mesylate
l Crizotinib, Pemetrexed, Docetaxel, Pemetrexed+ cisplatin, Pemetrexed + carboplatin, Alectinib, Ceritinib
m Pembrolizumab, Pembrolizumab + reduced dose ipilimumab, Nivolumab, Dacarbazine, Ipilimumab + dacarbazine, Ipilimumab, Novilumab + ipilimumab
n Nivolumab, Dacarbazine or paclitaxel + carboplatin, Ipilumab
o Vemurafenib, Dacarbazine, Dabrafenib, Dacarbazine, Trametinib, Dacarbazine or paclitaxel, Vemurafenib, Vemurafenib + cobimetinib, Dabrafenib + trametinib
p Vemurafenib, Dabrafenib + trametinib
Abbreviations: 5-FU = fluorouracil; ALK = anaplastic lymphoma kinase; CR = complete response; EGFR = epidermal growth factor receptor; ePAS = extended primary analysis set; FOLFIRI = folinic acid (leucovorin calcium) + fluorouracil + irinotecan; FOLFOX = folinic acid (leucovorin calcium) + fluorouracil + oxaliplatin ; FOLFOXFIRI = folinic acid (leucovorin calcium) + fluorouracil + oxaliplatin + irinotecan; FUOX = fluorouracil and oxaliplatin; IFL = folinic acid (leucovorin calcium) + fluorouracil + irinotecan; NR = not reported; OS = overall survival; PFS = progression-free survival; PR = partial response; XELOX = capecitabine + oxaliplatin
Source: Response to Day 150 Question 76, Table 3 (efficacy, 30 JUL 2018).

2.5.3. Discussion on clinical efficacy

The efficacy assessment is based on the pooled interim data from three currently ongoing trials; a dose-finding phase 1/2 study in adults with or without NTRK gene fusions (LOXO-TRK-14001), a phase 2 basket trial in adolescent and adult patients with NTRK fusions (LOXO-TRK-15002), and a dose-finding phase 1/2 study in paediatric patients with NTRK fusions (LOXO-TRK-15003). All studies are open-label without parallel comparator.

Design and conduct of clinical studies

Study LOXO-TRK-14001 was initiated in 2014. By the time Study LOXO-TRK-15002 and LOXO-TRK-15003 started in the 3rd quarter of 2015, there were several substantial changes made to the design of Study LOXO-TRK-14001, including changes in inclusion and exclusion criteria, number of patients, dose regimen, schedule of events, concurrent medication, etc.

Study LOXO-TRK-15002 was originally planned as a phase II open label basket study of the oral TRK inhibitor LOXO-101 in subjects with NTRK fusion-positive tumours. The study included 8 cohorts of patients with tumours bearing NTRK fusions, including non-small cell lung cancer, thyroid cancer, sarcoma, colorectal cancer, salivary gland cancer, biliary cancer, and primary CNS tumour, as well as a cohort that enrolled patients not included in the histologies listed above. The sample size for each cohort was planned using Simon's two-stage design (with 7 patients in the first stage and 11 patients in the second stage). Each cohort was to be continued or discontinued independently of the others. No pooling within or between studies were planned in the original protocol. Several changes were subsequently made to this plan.

After interaction with national agencies in April 2016, the applicant decided to pool all cohorts except for the CNS tumours cohort for analysis in the MAA. This was not explicitly stated in a protocol amendment for the study. In 2017 the Applicant further changed the strategy for MAA to pooling of data across studies LOXO-TRK-14001, LOXO-TRK-15002 and LOXO-TRK-15003 to serve as the primary efficacy dataset for the MAA. This issue has partly been addressed on request by analysing all possible selections of cohorts from the three studies. The estimated ORR in the ePAS population is in the upper end (the 90th percentile) of the distribution of possible estimates indicating a possible selection bias. On the other hand, as the applicant points out, a large majority of all possible ORR estimates are above 50% indicating an effect of substantial magnitude.

The small sample sizes in the LOXO-TRK-14001 and LOXO-TRK-15003 studies were in line with the exploratory nature of the studies, and rarity of the paediatric NTRK fusion cancers (LOXO-TRK-15003). The sample size of the pooled analysis is also small; the largest cohorts include 17, 13 and 10 subjects, respectively, and in several cohorts the sample size is smaller than the first stage of the Simon's 2-stage design in LOXO-TRK-15002. However this was justified on the basis of the pooled analysis. With the resulting small samples in most of the cohorts it is difficult to draw conclusions on homogeneity of possible effects between tumour types.

The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC). Tumour responses were assessed by the investigator using RANO or RECIST v1.1 criteria. The point estimates of the ORR were calculated based on the maximum likelihood estimator (i.e., crude proportion of patients with best overall response of confirmed CR or PR) based on the Full Analysis Set. The presentation of the efficacy results is in many cases misleading as the table titles and headings say Full Analysis Set, while the rates are calculated based on non-missing or "evaluable" data. An alternative presentation of ORR was presented on the Agency's request, with the denominator for the response rates based on the analysis sets deemed to be as close to the ITT as possible, resulting in ORR estimates that are above 50%. Also, additional

information was requested overall and by cohort for individual studies and pooled analysis for the ePAS population not excluding the CNS cohort, and for all available up-to-date data. This provided an explicit numerator and denominator for the number of responders (CR+PR) and the denominator as number with TRK. Although there were in total 137 patients with documented TRK fusions (as determined by local testing, including patients with primary CNS tumours, who received at least 1 dose of larotrectinib, and were recruited until 30 July 2018), there were 28 patients who have had insufficient follow-up time at the date of cut-off and were not included in this analysis. The ORR estimates by cohort were generally in line with the corresponding results in the ePAS analysis, showing no or limited evidence of efficacy of the VITRAKVI treatment in several tumour types.

The Applicant was requested to present a summary of all individual patients that were excluded due to lack of IRC data. Among the 28 patients excluded for this reason, 27 had treatment ongoing; range for duration of therapy was 0-4.7 months. One patient had discontinued treatment due to surgery after 4.3 months of larotrectinib treatment. This is a reassuring overall pattern as it does not indicate that patients with poorer outcomes were selectively excluded from the pooled analyses.

Patients included in all studies were required to have a locally advanced or metastatic solid tumour (i.e. carcinoma or sarcoma). Primary CNS malignancy was specifically mentioned and allowed in Studies 15002 and 15003. Patients must have received prior standard therapy or would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy (Study 15002); or must have progressed on prior therapy or was nonresponsive to available therapies and for which no standard or available systemic curative therapy existed (Studies 14001 and 15003); or, for infantile fibrosarcoma, would require disfiguring surgery or limb amputation to achieve a complete surgical resection (Study 15003).

Study 15002 appears to have somewhat less restrictive inclusion criteria in terms of prior therapy compared to the phase 1/2-studies, since progression on prior therapy was not required. This could thus encompass 1st line treatment. Also the wording in the inclusion criteria for studies 14001 and 15003 "for which no standard or available systemic curative therapy exists" appear to allow any line of treatment in patients with metastatic tumours, since these are generally not considered curative by any treatment modality. With regard to locally advanced tumours, it is often at least theoretically possible that the tumour might become resectable after effective systemic therapy and thus curable. Patients with and without documented NTRK gene fusion were allowed to participate in Study 14001 and Study 15003. Patients enrolled to Study 15002 were required to have TRK fusion positive cancer.

Efficacy data and additional analyses

The two dose-finding studies (14001 and 15003) which included patients without *NTRK* gene fusions as well as patients with tumours harbouring the drug target (the resultant TRK fusion protein) provide important contributions to the evidence base for larotrectinib's mechanism of action and clinical rationale. In Study 14001, only 1 (2%) PR (seen in a patient with a total tumour burden of 11 mm) and no CR were observed in patients with TRK fusion-negative tumours (n=62), in contrast with the high ORR (by INV) of 88% (7/8) among TRK fusion–positive patients. In study 15003, the ORR (by INV) among 26 fully evaluable patients at the time of data-cut off (excluding 2 patients with unconfirmed responses from the analysis) was 81% (21/26), while no objective responses were observed in the patients with TRK fusion-negative tumours. IRC was apparently not performed for the TRK-fusion negative patients. Nevertheless, these comparative data showing high response rates in *NTRK* fusion-positive groups and essentially no responses in *NTRK* fusion-negative patients, provide clinical support of the proposed mechanism of action and the selectivity of the effect to patients harbouring the drug target. The rationale for restricting the indication to patients with demonstrated *NTRK* gene fusions is considered justified based on these data.

The choice of target dose for approval was not based on a maximum tolerated dose, or a thorough investigation of maximum efficacy. It was based on sufficiently high efficacy in combination with an acceptable safety profile, supported by PK data. Subsequent to the selection in Study 14001 of the dose 100 mg BID in adults for further development, the dose step 150 mg BID was cleared, and also the 200 mg BID cohort did not fulfil MTD criteria with only 1/6 patients experiencing a DLT.

With regard to the paediatric dose, from an efficacy point of view, the presently available data (ePAS2) indicate a high degree of activity, with ORR at 82% in the overall paediatric population (<18 years), and in the lower age groups 1-month to < 2 years the ORR was 100% (12/12); in the 2 to<6 years it was 86% (6/7).

The main efficacy analysis set is the pooled "extended primary analysis set 2", ePAS2, which consists of 93 patients from the studies 14001, 15002 and 15003, who had: a NTRK gene fusion, measurable disease, and received at least 1 dose of larotrectinib. Patients with primary CNS tumours were excluded from the ePAS2. These patients were required to have received prior standard therapy appropriate for their tumour type and stage of disease or who, in the opinion of the investigator, would have had to undergo radical surgery (such as limb amputation, facial resection, or paralysis causing procedure), or were unlikely to tolerate, or derive clinically meaningful benefit from available standard of care therapies in the advanced disease setting.

At the time of data cut-off 57% have treatment ongoing and 31% have experienced disease progression. The median time on treatment is 12.1 months and 52% of patients in the ePAS had time on treatment for 12 months' or more. Only 14 patients (15%) have died, and 34 patients (37%) have had a PFS-event (death or disease progression).

The ORR by IRC was 72% (n=67/93, 95% CI: 62, 81%), and ORR by investigator assessment (INV) was 80%. The single-arm, open-label setting allowing for potential investigator bias is noted. The agreement rate between IRC and INV assessments was 90%. These overall ORR results are considered outstanding.

In view of the post-hoc pooling of patients across studies with different original purposes, it is noted that the INV ORR was 61% in the Phase-2 basket trial, compared with 81% and 88% in the phase-1/2 studies with dose-finding and proof-of principle aims (at previous data cut-off). It is also noted that in the previously submitted data from the ePAS (n=73) at a shorter follow-up (19 Feb 2018), 88% of responding patients had a response that lasted 6 months or more, and 72% 12 months or more. The corresponding results were reduced in the latest update (30 Jul 2018). Thus, in the ePAS2, 72% of responding patients had a response duration of 6 months or more, and 42% 12 months or more. This illustrates how limited early data can overestimate the true treatment effects. Similarly, the ORR in the paediatric subset (<18 years) was reduced from 90% in the ePAS to 82% in the ePAS2.

The median time to response (TTR) was short and very consistent at 1.8 months by IRC and INV, respectively, in the ePAS2 as well as in previous versions of the pooled analysis sets (PAS, and ePAS). The ePAS2 IRC 25th, 75th percentiles were 1.71 and 1.94 months, respectively. A vast majority of responding patients responded at the first tumour evaluation.

The median duration of response (DoR) was not estimable in any of the individual studies (at previous data cut-off) or in the main analysis population, ePAS2, which is consistent with the high proportion of patients still in response, 73-86% in the individual studies (INV); 70% in the pooled ePAS2 population (IRC and INV).

Thus, of the 67 responding patients according to IRC, 47 (70%) were still in response at the time of analysis. The median time on treatment was 12.1 months, however; thus, among the presently included patients the median DoR is likely around 12 months. This would generally be considered a long duration of response regardless of line of treatment in any/most metastatic solid tumours. (It should be noted that

a small number of patients continued larotrectinib post-progression, and contributes to the time on treatment.)

The progression-free survival (PFS) median event-rate was low at 37% (IRC) and 38% (INV) in the ePAS2, and the median was 27.4 months (95% CI: 13.8, NE) by IRC and 28.3 months (95% CI: 15.2, NE) by investigator assessments. The PFS rate at 6 months was 77%, and the PFS rate at 12 months was 64% (95% CI: 51, 76%) by IRC.

The overall survival (OS) median was not reached in the ePAS2 as a result of the present very low event-rate of 15% (14/93 dead). The OS median follow-up time was 16.7 months (25th, 75th percentiles: 9.3, 23.0 months). The OS rate at 12 months was 88% (95% CI: 81, 95%). Beyond approximately 28 months, less than 10 patients remain in the K-M plot. At this point, OS survival portion appears to be around 80%. The OS and PFS data are immature at 15% and 37% event rate, respectively, in the ePAS2 population. In the CNS group, all 9 patients are still alive. These patients had received prior cancer treatment (surgery, radiotherapy and/or previous systemic therapy).

PFS and OS are important for contextualisation of the ORR and DoR results and in relation to approved anticancer products normally approved based on PFS and/or OS. However, due to the pooling of many different types of primary malignancies with inherently different prognosis, the data should be interpreted with caution.

Subgroup analyses

The objective response rate was highly variable across the studied tumour types, from 0% ORR in single patients with breast cancer, cholangiocarcinoma and pancreatic cancer to 100% in the 4 patients with GIST. Tumour types where NTRK gene fusions are characteristic (or even considered pathognomonic) of the disease, such as Infantile fibrosarcoma (IFS, n=13), Salivary gland/MASC (n=10), and congenital mesoblastic nephroma (n=1), tended to have higher ORR (92%, 80%, and 100%, respectively). However, these estimates are not robust due to the small sample sizes of individual subgroups.

Patients with primary CNS tumours were excluded from the pooled primary analysis populations, based partly on preclinical findings. Among 9 patients with primary CNS tumours who were excluded from the ePAS2 based on tumour type, but fulfilled the other criteria, 1 had an objective response (PR); the remaining 7 had SD as best response, 3 had numerical tumour size decrease, 3 has had disease progression and 6 are ongoing without progression. The initial application did not include patients with primary CNS tumours in the indication for Vitrakvi, however since there is no scientific rationale to exclude this previously treated patient population with no satisfactory treatment options available, the CHMP considered that the indication should also cover patients with primary CNS tumours. Further data are expected post authorisation (see SOBs).

The ORR (IRC) was 68% (95% CI: 55, 79%) for patients with age ≥ 18 years (n=65); and 82% (95% CI: 63, 94%) for patients with age < 18 years (n= 28). Patients aged ≥ 65 years (n=15) had a response rate of 56% (95% CI: 31, 78%). It should be noted that age groups co-vary with tumour type.

In view of the uncertainties concerning the paediatric dosing based on body surface area, it is noted the in the age group 1-month to < 2 years the ORR was 100% (12/12); and in the age group 2 to <6 years it was 86% (6/7). In the next age group, 6 to <12 years, 2/6 patients (33%) had an objective response.

The exposures were similar in responders and non-responders, in adults and in patients <18 years of age.

The ORRs per NTRK fusion type was 63% (95% CI: 47, 78%) for *NTRK1* (n=41), 33% (95% CI: 1, 91%) for *NTRK2* (n=3), and 82% (95% CI: 68, 91%) for *NTRK3* (n=49).

Out of 55 patients in the PAS population, 17 had PD after an initial response; from 10 of these the sponsor obtained post-progression biopsies. In 8/10 patients NTRK resistance mutations were detected and in the

remaining 2 patients, BRAF V600E mutations were identified. However, based on additional information, one of these patients also had a NTRK resistance mutation, and the other had very low levels of the BRAFV600E mutation (<1% allelic fraction) in circulating tumour DNA, hampering the interpretation of the role of the BRAF mutation. These NTRK resistance mutations affect the kinase solvent front and the xDFG motif. Structural modelling suggests that each mutation directly interferes with binding by both larotrectinib and all other first-generation TKIs with TRK activity. Functional studies have subsequently confirmed that cancer cells harbouring these mutations are cross-resistant to all TKIs with anti-TRK activity. Clinical trials are ongoing with second-generation TRK inhibitors (such as LOXO-195) that have been shown to be able to overcome the acquired NTRK mutations. Secondary NTRK mutations altering the kinase domain of TRK thus appear to be a/the major acquired resistance mechanism to larotrectinib. Information has been included in the SmPC. Furthermore, the Applicant has agreed to amend the NAVIGATE study to investigate resistance mechanisms in post-progression biopsies.

NTRK fusion detection

Larotrectinib is a targeted therapy and its activity is shown to be highly selective to tumours harbouring an NTRK fusion. Correct detection of this fusion is therefore paramount. Molecular pathology reports were provided for 105 enrolled on larotrectinib studies 14001, 15002 and 15003 who fulfilled the criteria for data pooling. The 105 molecular pathology reports documented the results of 33 unique tests performed at 31 different labs. Most of the tests performed were NGS-based (N = 98), while the minority were FISH-based (N = 6) and RT-PCR-based (N=1).

The SmPC states that "the presence of an NTRK gene fusion in a tumour specimen should be confirmed by a validated test prior to initiation of treatment with VITRAKVI".

Clinical data supporting a histology-independent indication

As the NTRK fusion is rare in more common tumour types, there is still limited information on the level of efficacy in some otherwise common tumour types, such as non-secretory breast cancer, melanoma and colorectal cancer. A lower ORR was observed in these histologies as well as a shorter duration of response (DoR) compared to other responding tumour types but the numbers are too small to draw any conclusions.

Regarding potential differential resistance mechanisms across tumour histologies, the BRAF example of differential additional pathways in different tumour types (melanoma and colorectal cancers) causing responses in one but not the other is well-known. Among the 14 patients in the ePAS2 who had PD or SD less than 4 months as their best response (i.e. signs of little or no activity), 2 had an additional oncogenic driver in their tumour. (The single patient with breast cancer had an AKT E17K mutation, and one patient with mixed histology thyroid cancer had a BRAF V600E mutation concomitantly with the NTRK fusion. Both had PD.) However, such potential drivers (of other types) were also seen in patients with CR and PR (e.g. Flt3-IDT, FGFR1 and PIK3CA, Table 69). In addition, a large variation of molecular alterations, involving e.g.TP53, PTEN, and CDKN2A/B were frequently seen in the ePAS2 in responding and non-responding patients alike. No conclusions can be drawn based on the single occurrences of known oncogenic drivers across patients with and without tumour response, respectively. The BRAFV600E mutations might be an exception, since it was also observed in 2/10 patients with PD after initial response (i.e. acquired resistance) for whom post-progression biopsies were available, while the remaining 8 patients had NTRK mutations causing resistance.

Indication elements

The indication recommended by the CHMP is:

"VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display 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 no satisfactory treatment options (see sections 4.4 and 5.1).*

The benefit of VITRAKVI has been established in single arm trials encompassing a relatively small sample of patients whose tumours exhibit *NTRK* gene fusions. Favourable effects of VITRAKVI have been shown on the basis of overall response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on tumour type, as well as on concomitant genetic alterations. For these reasons, VITRAKVI should only be used if there are no treatment options for which clinical benefit has been established, or where such treatment options have been exhausted (i.e., no satisfactory treatment options).

The wording "have no satisfactory treatment options" was chosen in order to allow treatment decisions to select the optimal treatment for a patient with an NTRK gene fusion based on a benefit/risk evaluation, and allow taking into account that some established therapies could have a low likelihood of benefiting a given patient based on poor tolerability or limited efficacy. For tumour types where clearly effective options for a given patient are available, larotrectinib would be used after all acceptable treatment options have been exhausted. The word satisfactory thus allows the bypassing of therapies of limited efficacy that are currently nevertheless recommended in therapy guidelines (in the absence of more effective treatments). This is considered appropriate, given the high likelihood of (early and durable) response from larotrectinib in most of the studied tumour types and the favourable safety profile.

This possibility to bypass established therapy options could be a risk, however, if therapies that are known to confer an overall survival benefit are disregarded, considering that at this time, based on non-comparative larotrectinib trials, no OS advantage over available therapies has been established. In other words, there could be a risk of an indication "drift" towards earlier lines of therapy for which a positive B/R was not established. The CHMP nevertheless considers that the magnitude of effect in terms of ORR and DoR and the early timing of responses reduce this risk. The Applicant will submit a global non-interventional study where drug utilisation patterns can be studied (see RMP).

The surgical morbidity criterion "or where surgical resection is likely to result in severe morbidity" is derived from paediatric study LOXO-TRK-15003 (Study 15003) that included patients with locally advanced infantile fibrosarcoma "that would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection". A total of 8 patients met this criterion. These eight patients had resectable disease which, had the resection occurred, would have led to limb amputation (in 2-3 cases) or anticipated permanent motor or sensory deficits. In one case, the reason for larotrectinib was noted as inability to obtain clear margins [if surgery was to be performed]. Out of 8 patients, 2 achieved CR (radiological), 2 had surgical CR – both taken off larotrectinib, 3 had PR (radiological), and 1 was resected without achieving complete resection. All who achieved radiological PR and CR continued on larotrectinib therapy. It is acknowledged that some patients presenting with a disease in which cure through surgery is the therapeutic goal, could have a better outcome with cytoreduction of the tumour with larotrectinib followed by surgical resection, thus avoiding disfiguring amputation and permitting limb salvage.

Additional expert consultation

The Scientific Advisory Group (SAG) in Oncology, and the EMA Biostatistics working party (BSWP) were consulted during this procedure.

CHMP questions with SAG answers[12]

1. Do available data support the assumption that NTRK gene mutations are driver mutations, that the mechanism of action is independent of tumour type/histology, and that hereby larotrectinib is likely to exhibit clinically relevant activity in tumours expressing NTRK fusion proteins regardless of the tissue of tumour origin?

The SAG agreed by consensus that available data do not support the hypothesis that NTRK gene fusions are universally oncogenic "drivers", independently of tumour type/histology and other disease characteristics; that the relevance of the mechanism of action may differ according to these and other characteristics; and that the non-clinical and clinical data are insufficient to establish activity regardless of tumour type and other characteristics. In some paediatric malignancies preclinical and clinical data support NTRK as an oncogenic driver. Specifically fusion genes affecting NTRK1/2/3 are highly recurrent in certain rare malignancies. The best known form of NTRK fusion gene is the ETV6-NTRK3, which is present in >95% of secretory carcinomas of the breast [1], mammary analogue secretory carcinoma (MASC) of the salivary glands [2], congenital fibrosarcoma [3] and cellular mesoblastic nephromas [4]. During the initial discussion, one expert raised the possibility to have a tissue independent approval for cancers with proven NTRK fusions as oncogenic "drivers", provided that next generation sequencing (NGS) could exclude other alterations being significant drivers for tumour progression. However, data are lacking to establish the efficacy of such possible strategy (see also answer to question No. 3). Another expert expressed concern for the very low percentage of breast cancers having proven NTRK fusions as "oncogenic driver".

Concerning the biological rationale, there are only few tumour types (listed above) for which NTRK fusions have been established as oncogenic "drivers" regardless of other characteristics. Larotrectinib has also shown important activity in GIST with NTRK after resistance/relapse with imatinib (ORR=5/5) and this likely reflects a similar role for NTRK fusions. For these conditions, given the strong rationale and the available clinical data (for some of these conditions, salivary gland ORR=15/17; infantile fibrosarcoma ORR=12/13; congenital mesoblastic nephroma ORR=1/1) and based on reasonable extrapolations, it possible to conclude that efficacy has been established in the absence of available treatments of proven efficacy in terms of convincing clinical efficacy endpoints.

However, confirmatory evidence on tumour biology (as close as possible to treatment initiation) and clinical outcomes should be provided.

For other conditions, the role of NTRK fusions as oncogenic "drivers" is not properly studied and well-established. There are insufficient data to establish the activity of larotrectinib due to lack of comprehensive sequencing of tumour tissue prior to treatment, the small sample size in different tumour types, the significant heterogeneity observed in terms of ORR coupled with the notably very low ORR observed in different tumour types (ORR=0%-33%), especially in those common tumour types where occurrence of NTRK gene fusion is rare (lung, colon, breast).

[12] References:

1. Tognon C, Knezevich SR, Huntsman D et al. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. Cancer Cell 2002; 2: 367-376.
2. Skalova A, Vanecek T, Sima R et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. Am J Surg Pathol 2010; 34: 599-608.
3. Knezevich SR, McFadden DE, Tao W et al. A novel ETV6-NTRK3 gene fusion in congenital fibrosarcoma. Nat Genet 1998; 18: 184-187.
4. Knezevich SR, Garnett MJ, Pysher TJ et al. ETV6-NTRK3 gene fusions and trisomy 11 establish a histogenetic link between mesoblastic nephroma and congenital fibrosarcoma. Cancer Res 1998; 58: 5046-5048.

2. For which, if any, histologies is the prognostic impact of NRTK fusion proteins presently understood? Does the prognostic impact differ depending on the gene fusion partner?

The association between the NTRK-fusions or the fused NTRK genes and prognosis in terms of long-term clinical outcomes is not generally well-understood due to very limited data except for the rare tumour types listed above where the fusion proteins are considered indicative of the disease (pathognomonic).

3. Does the proposed indication statement adequately cover those patients for whom treatment with larotrectinib would be clinically reasonable, and exclude those for whom it would not?

The proposed indication encompassing all solid tumours independently of tumour type does not reflect the conditions where efficacy has been established based on available data or reasonable extrapolations. In addition, however, one can note that larotrectinib has demonstrated an acceptable safety profile, albeit the number of exposed patients is low. In conclusion, evidence-based clinical decisions to use larotrectinib are only justified for the rare conditions listed above and in situations where established alternatives are lacking or, as in the case of major surgical procedures, where available alternatives are associated with high morbidity and mortality.

From a clinical decision perspective, use of larotrectinib may be an attractive therapeutic option when established effective treatments are lacking and when based on relevant tumour tissue sequencing one could confirm the presence of NTRK-fusions and exclude other known oncogenic "drivers". However, such decisions cannot be considered evidence-based due to the lack of clinical evidence and the lack of predictive ability of clinical decision algorithms purely based on sequencing data. Nevertheless, such approaches warrant further investigation.

4. What additional (non-)clinical studies might be relevant to further confirm the assumption of tissue-independent activity of larotrectinib?

A main drawback of the studies presented was the lack of comprehensive sequencing (NGS) of relevant tumour tissue reflecting the tumour characteristics at the time of treatment with larotrectinib. Such studies are necessary to understand the role of NTRK fusions in the context of other disease characteristics to allow patient selection and further evidence-based development in other indications or across groups of tumour types. Although the burden associated with biopsies is well-recognised most patients understand its importance and are willing to undergo the procedure. Liquid biopsies should be further investigated to address this challenge; these should be performed in projects with a joint tumour biopsy up-front and ideally at cancer progression. For the rare indications listed above, such studies should be conducted to refine the understanding on patient selection.

Retrospective analyses on the prognostic implications based on relevant tumour samples collected at the time of last progression prior to larotrectinib treatment, should also be conducted, if possible.

Retrospective data should also be obtained on the prognostic implications for different NTRK fusions derived from large institutions/ large population based registries, as once demonstrated for c-ERBB2 (Her-2). The therapy predictive value for larotrectinib should then be firmly established, including multivariate analyses including other relevant prognostic factors/predictors.

Furthermore, there is a need to confirm the activity for many of the listed conditions, following all patients for long-term outcomes. Such studies should be conducted as interventional studies adhering to rigorous response adjudication (RECIST); "real-life" non-interventional studies may not be sufficient to draw valid conclusions.

To further develop the product across other tumour types, or to establish independence from tumour type, it is important to collect convincing biological and clinical evidence to understand the resistance

mechanisms involved, especially primary resistance, the role of concomitant biological and other characteristics that may explain the observed heterogeneity or lack of activity, and to confirm any reasonable extrapolations using reasonably powered studies to detect sufficient activity in different tumour types, in particular the more common cancers.

Studies should also continue with the purpose to analyse activity, as determined by e.g. tyrosine phosphorylation assays, of other NTRK-fusion-gene products than those already analysed. Also, data should be collected regarding the ability of larotrectinib to block kinase activity of other NTRK-fusion-gene products than those already analysed.

Further non-clinical studies should also be conducted to better understand fusion protein regulation and activity in the presence of other activated relevant genes/suppression of tumour suppressors which may modify the effect by larotrectinib.

A wide array of different techniques can be employed in the detection of NTRK1/2/3 rearrangements. In the available and ongoing clinical studies gene rearrangements have been assayed by fluorescence in situ hybridization (FISH) and reverse transcriptase (RT)-PCR, and FISH assays for the detection of the ETV6-NTRK3 fusion gene are commercially available. However, given the multitude of 5' partners involved in NTRK1/2/3 fusion genes, assays that allow for the detection of multiple variants in a single test, including NGS-based RNA and DNA approaches, have been widely used in large academic centres. The adoption of these NGS-based methods seems to be the better option despite testing can also be performed with immunohistochemistry followed by confirmatory NGS. Data on sensitivity and specificity on all available essays should be made available.

Further to the SAG responses, the CHMP considered the limitations of data and uncertainties in respect to efficacy in different tumour type subgroups are agreed and have been previously identified during the procedure. However, recognising certain degree of heterogeneity in response is unavoidable in the same way as there will be important effect modifiers within the scope of any indication, including those based on histology and other patient, disease or treatment characteristics. Thus, the critical issues are whether the studies are representative of the treated population once the product is authorised and what uncertainties are acceptable given available data and the intended use – in this case as a last line treatment in patients without satisfactory treatment options.

The CHMP also sought advice from the CHMP Biostatistics working party (BSWP).

The request to the BSWP concerned the statistical principles to be applied in the analysis of data to determine that a certain tissue of origin is a genuine outlier with respect to objective responses.

Additional efficacy data needed in the context of a conditional MA

Due to the limited size of the efficacy database, including uncertainties due to the single arm nature of the studies, the presently available efficacy data for larotrectinib are not considered comprehensive.

The main areas of non-comprehensive data with regard to efficacy are:

- The benefit in subgroups of patients based on histology. This may be studied in terms of ORR and DoR in prospective single-arm studies encompassing a broad variety of tumour types.

- The requirement for unbiased estimate of ORR and DoR. This may be studied in a prospective cohort study.

- The size of treatment benefit on time-dependent outcome measures (OS, PFS);

- Resistance mechanisms and the role of concomitant oncogenic drivers to further characterise efficacy in different subgroups.

In order to fulfil a comprehensive data package, the Applicant as part of study LOXO-TRK-15002 (NAVIGATE) will submit a prospective cohort of 75 patients, for which at least 1 year of follow-up is available, and will perform an overall pooled analysis where the target population includes the ePAS2/SAS3 cohort (with the updated data) along with the prospective cohort, which would give increased precision of the estimates for the ORR and DoR.

In addition, the applicant will enrol at least 9 and up to 20 patients in total in each of the identified common tumour type subgroups (lung, melanoma, colorectal cancer, non-secretory breast), and pre-specifies rules for conclusions of adequate/inadequate clinical activity. A Bayesian approach, using non-informative prior distribution for ORR is proposed. The posterior probability for ORR is calculated to be ≥ 10%. If all of the first 9 patients fail to respond then posterior probability of adequate clinical activity is <0.2.

The applicant will continue enrolment in the prospective cohort for 36 months post approval. The plan is to enrol 200 patients (75 already enrolled) including 80 in the common tumour types and 120 in the other tumour types and would discuss with the Agency whether enrolment should continue.

Furthermore, the applicant will review the relevance of clinical efficacy in a given histology in case of no responses in 9 patients. If that occurs in the prospective cohort, the applicant should alert the Agency. In order to decide whether "inadequate response" has been identified in certain tumour types, the applicant will follow a Bayesian approach as a methodological rule and conventional approach. The applicant will inform the Agency if the criteria of "inadequate response" according to the Bayesian approach is fulfilled for any particular histology.

2.5.4. Conclusions on the clinical efficacy

Overall, notwithstanding the considerable methodological caveats outlined above, the efficacy estimates available today may be considered outstanding in this generally late stage disease setting. The main issue efficacy-wise is the robustness and generalisability of these estimates. While it is likely that the estimates may change, possibly in a negative direction, the present outstanding estimates provide some reassurance as to the presence of a large treatment benefit. Important quantitative interactions between treatment and tumour type will be further explored.

Available data are thus considered non-comprehensive and a conditional approval is therefore considered appropriate.

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

- In order to further confirm the histology-independent efficacy of larotrectinib and to investigate the primary and secondary resistance mechanisms, the MAH should submit a pooled analysis for the increased sample size including the final report of study LOXO-TRK-15002 (NAVIGATE).

2.6. Clinical safety

The initial submission with data cut-off date of 19 February 2018 included an integrated, pooled safety set named the "Overall Safety Analysis Set" (N=176) comprising data from all adult and paediatric patients who had a malignancy with or without a documented NTRK gene fusion and who received at least one dose of larotrectinib in studies LOXO-TRK-14001 (≥18 years of age, N = 70), LOXO-TRK-15002 (acronym NAVIGATE, ≥ 12 years of age, N = 63), and LOXO-TRK-15003 (acronym SCOUT, paediatric population, N = 43). Notably, the pooled safety set did not distinguish data between adults and paediatric patients nor according to the recommended larotrectinib dose. A safety update with a new cut-off date of 30 July 2018, has provided an additional 5.5 months of follow-up and with an increase in number to a total

of 56 paediatric and 152 adult patients. This update also includes data presented separately for the adult and paediatric population treated with the recommended dose and data according to the respective paediatric age-cohorts.

The safety assessment is based on data with the data cut-off date of 30 July 2018 unless otherwise specified.

Patient exposure

Table 77: Patient Disposition by Analysis Set as of the Data Cut-off 30 Jul 2018

Status	Efficacy-eval NTRK Fusion Cancers (N=82)	Overall NTRK Fusion Cancers Safety (N=125)	Overall Safety (N=167)
Progression of Disease[4,5]			
No	51 (62%)	89 (71%)	97 (58%)
Yes	31 (38%)	36 (29%)	70 (42%)
Treatment Continued Post-Progression			
Yes	14 (17%)	16 (13%)	18 (11%)
Treatment Status[4]			
Discontinued	35 (43%)	39 (31%)	81 (49%)
Continuing	47 (57%)	86 (69%)	86 (51%)
Reason Treatment Discontinued[4]			
Protocol Deviation	2 (2%)	2 (2%)	2 (1%)
Disease Progression	27 (33%)	30 (24%)	63 (38%)
Adverse Event	2 (2%)	2 (2%)	7 (4%)
Subject Decision	2 (2%)	2 (2%)	5 (3%)
Other	2 (2%)	3 (2%)	3 (2%)
Death	0 (0%)	0 (0%)	1 (1%)
Time on Treatment[4]			
Less than 3 months	13 (14%)	34 (25%)	89 (43%)
3 to <6 months	10 (11%)	23 (17%)	31 (15%)
6 to <9 months	14 (15%)	19 (14%)	24 (12%)
9 to <12 months	8 (9%)	9 (7%)	11 (5%)
12 to <15 months	13 (14%)	15 (11%)	15 (7%)
15 to <18 months	7 (8%)	7 (5%)	7 (3%)
18 to <21 months	7 (8%)	8 (6%)	8 (4%)
21 to <24 months	6 (6%)	7 (5%)	7 (3%)
24 or more months	15 (16%)	15 (11%)	16 (8%)
Time on Treatment (months)			
N	93	137	208
Mean	13.5	10.6	7.9
Standard deviation	9.6	9.4	8.8
Median	12.1	7.5	4.1
Minimum	0.66	0.03	0.03
Maximum	40.7	40.7	40.7

[1] Initial NDA visit cutoff date 17-Jul-2017.
[2] Adults (18 years and older).
[3] Pediatrics (< 18 years). For Cohorts 1 and 2, the target was based on dosing calculation tables in Appendix C of Protocol 15003. For Cohort 3, the target dose was capped at 100 mg BID.
[4] Status as of 30-Jul-2018.
[5] Disease progression includes patients with clinical progression.
Percentages are calculated based on the number of patients in the column heading as the denominator.

At the new data cut-off date, 94 (45%) of the patients in the Overall Safety set (N=208) and 93 (68 %) of the patients in the Overall NTRK Fusion Cancers set (N=137) were still on study treatment. The most common reasons for discontinuation was disease progression (87 patients [42 %]). Overall the low number of patients that discontinued study drug due to AEs is recognised (overall $\leqslant$ 4 %).

Duration of Larotrectinib Dosing

Table 78: Median time on larotrectinib treatment

Analysis set	Updated analysis Cut-off 30 JUL 2018	Originally submitted analysis
Overall Safety Analysis Set	4.1 (N=208)	3.7 (N=176)
All NTRK Fusion Cancers	7.5 (N=137)	7.4 (N=105)
ePAS2 (N=93)	12.1	N/A
SAS1B (N=20)	7.3	N/A
ePAS (N=73)	14.5	10.2
PAS (N=55)	18.2	13.8

N/A = not applicable

Source: Tables 14.01.02 (efficacy), 14.01.02 (safety), and 14.01.02.01(efficacy); original Module 5.3.5.3, ISS_19 FEB 2018, Table 14.1.2; original Module 5.3.5.3, ISE_19 FEB 2018, Table 14.1.2

Dose modifications

Table 79: Study Drug Dosage Modifications (cut-off: 30 Jul 2018)

Status	Efficacy-eval NTRK Fusion Cancers (N=82)	Overall NTRK Fusion Cancers Safety (N=125)	Overall Safety (N=167)
Any Dosage Modifications			
Yes	70 (85%)	100 (80%)	133 (80%)
No	12 (15%)	25 (20%)	34 (20%)
Modification Type[1]			
Dose missed, skipped, or delayed	68 (83%)	97 (78%)	130 (78%)
Dose reduced	17 (21%)	19 (15%)	27 (16%)
Dose increased	18 (22%)	24 (19%)	24 (14%)
Reason for Dose Reduction[1]			
Adverse event	10 (12%)	10 (8%)	16 (10%)
Other reason	8 (10%)	10 (8%)	12 (7%)
Reason for Dose Increase[1]			
Protocol violation	1 (1%)	2 (2%)	2 (1%)
Adverse event	0 (0%)	1 (1%)	1 (1%)
Other reason	17 (21%)	23 (18%)	23 (14%)
Reason Dose Skipped, Missed, Delayed[1]			
Adverse event	32 (39%)	44 (35%)	65 (39%)
Protocol violation	31 (38%)	42 (34%)	43 (26%)
Other reason	45 (55%)	63 (50%)	88 (53%)

[1] Patients may be counted in more than one row.

Overall the vast majority of patients needed dose modifications (≥ 80 %). Dose reductions were needed for 15 % of the patients in the Overall Safety Analysis Set however dose reductions due to AEs were infrequent with a low proportion of 9 %. Reasons for dose increases were mainly due to increase in BMI/ weight gain.

Adverse events

Table 80: Overall Adverse Event Information (Larotrectinib Analysis Sets) by Analysis Set as of the Data Cut-off 30 Jul 2018

Status	Efficacy-eval NTRK Fusion Cancers (N=93)	Overall NTRK Fusion Cancers Safety (N=137)	Overall Safety (N=208)
Patients with TEAE	92 (99%)	133 (97%)	203 (98%)
Patients with TEAE Related to Larotrectinib	81 (87%)	114 (83%)	167 (80%)
Patients with TEAE Severity 3 or 4	51 (55%)	61 (45%)	103 (50%)
Patients with TEAE Severity 3 or 4 and Related to Larotrectinib	12 (13%)	14 (10%)	27 (13%)
Patients with TEAE and Action Taken of Larotrectinib Permanently Discontinued	5 (5%)	5 (4%)	23 (11%)
Patients with TEAE and Action Taken of Larotrectinib Permanently Discontinued and Related to Larotrectinib	1 (1%)	1 (1%)	5 (2%)
Patients with Serious TEAE	31 (33%)	38 (28%)	70 (34%)
Patients with Serious TEAE and Related to Larotrectinib	5 (5%)	7 (5%)	12 (6%)
Patients with Fatal TEAE	4 (4%)	4 (3%)	12 (6%)

TEAEs are defined as adverse events that start on or after the first administration of Larotrectinib. Page 1
Related events are those judged by the Investigator as related to Larotrectinib.
Severity grade assignment based on CTCAE (v4.03): Grade 3 (severe), Grade 4 (life-threatening).
Percentages are calculated based on the number of patients in the column heading as the denominator.

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Almost all patients in the Overall Safety Analysis set experienced at least one TEAE (98 %) with the vast majority of TEAEs considered related to study drug (80 %). Half of the study population experienced Grade 3 or 4 events with 13 % considered related to treatment. Reports of serious TEAEs were similar between the analysis sets, accounting for about 1/3 of the respective study populations. TEAE leading to treatment discontinuation were reported in 11 % in the Overall safety analysis set which should be compared with about 5 % in the NTRK Gene Fusion Cancer analysis sets.

By System Organ Class (SOC) in the Overall safety set, TEAEs were most commonly reported in the SOCs of Gastrointestinal disorders (70 % [Nausea 28 %]), General disorders and administration site conditions (63 % [Fatigue 36 %]), Nervous system disorders (62 % [Dizziness 29 %]), Musculoskeletal and connective tissue disorders (51 % [Myalgia 16 %]), Respiratory, Thoracic and Mediastinal disorders (51 % [Cough 26 %]), Metabolism and Nutrition disorders (50 % Decreased [appetite 13 %]), Investigations (48 % [AST and ALT increase 26 % each]), Infection and infestation (43 %), and Blood and lymphatic system disorders (41 % [Anaemia 26 %]).

Similar proportions were observed in the Overall NTRK Fusion Cancers set.

Table 81. TEAEs by Preferred Term in Decreasing Order of Frequency (Larotrectinib Analysis Sets), abbreviated

Preferred Term	Efficacy-eval NTRK Fusion Cancers (N=93)	Overall NTRK Fusion Cancers Safety (N=137)	Overall Safety (N=208)
Patients with TEAE	92 (99%)	133 (97%)	203 (98%)
Fatigue	37 (40%)	43 (31%)	74 (36%)
Dizziness	29 (31%)	40 (29%)	61 (29%)
Nausea	29 (31%)	39 (28%)	59 (28%)
Constipation	30 (32%)	40 (29%)	56 (27%)
Alanine aminotransferase increased	35 (38%)	47 (34%)	55 (26%)
Anaemia	28 (30%)	34 (25%)	55 (26%)
Aspartate aminotransferase increased	32 (34%)	43 (31%)	55 (26%)
Cough	33 (35%)	39 (28%)	54 (26%)
Vomiting	25 (27%)	32 (23%)	49 (24%)
Diarrhoea	29 (31%)	37 (27%)	48 (23%)
Pyrexia	21 (23%)	27 (20%)	38 (18%)
Dyspnoea	17 (18%)	19 (14%)	37 (18%)
Headache	19 (20%)	30 (22%)	35 (17%)
Myalgia	15 (16%)	24 (18%)	34 (16%)
Oedema peripheral	19 (20%)	22 (16%)	33 (16%)
Weight increased	19 (20%)	26 (19%)	30 (14%)
Arthralgia	13 (14%)	19 (14%)	29 (14%)
Abdominal pain	15 (16%)	18 (13%)	27 (13%)
Decreased appetite	8 (9%)	13 (9%)	27 (13%)
Pain in extremity	17 (18%)	21 (15%)	27 (13%)
Muscular weakness	12 (13%)	15 (11%)	26 (13%)
Back pain	17 (18%)	18 (13%)	25 (12%)
Nasal congestion	14 (15%)	20 (15%)	25 (12%)
Neutrophil count decreased	18 (19%)	21 (15%)	25 (12%)
Blood creatinine increased	10 (11%)	17 (12%)	22 (11%)
Leukocyte count decreased	14 (15%)	19 (14%)	22 (11%)
Hypertension	9 (10%)	11 (8%)	21 (10%)
Lymphocyte count decreased	7 (8%)	14 (10%)	21 (10%)
Upper respiratory tract infection	15 (16%)	20 (15%)	21 (10%)
Urinary tract infection	16 (17%)	16 (12%)	21 (10%)
Hypoalbuminaemia	8 (9%)	11 (8%)	20 (10%)
Dysgeusia	7 (8%)	11 (8%)	18 (9%)
Fall	10 (11%)	13 (9%)	18 (9%)
Blood alkaline phosphatase increased	9 (10%)	9 (7%)	17 (8%)
Hypokalaemia	7 (8%)	10 (7%)	16 (8%)
Dry skin	9 (10%)	12 (9%)	15 (7%)
Paraesthesia	9 (10%)	12 (9%)	15 (7%)
Hypotension	7 (8%)	11 (8%)	14 (7%)
Rash	9 (10%)	11 (8%)	14 (7%)
Abdominal distension	6 (6%)	8 (6%)	13 (6%)

Continued

Anxiety	7 (8%)	8 (6%)	13 (6%)
Asthenia	6 (6%)	8 (6%)	13 (6%)
Gait disturbance	5 (5%)	5 (4%)	13 (6%)
Hot flush	3 (3%)	8 (6%)	13 (6%)
Hypophosphataemia	6 (6%)	8 (6%)	13 (6%)
Insomnia	7 (8%)	8 (6%)	13 (6%)
Peripheral sensory neuropathy	10 (11%)	13 (9%)	13 (6%)
Platelet count decreased	7 (8%)	11 (8%)	13 (6%)
Pruritus	7 (8%)	9 (7%)	13 (6%)
Flatulence	11 (12%)	11 (8%)	12 (6%)
Hypocalcaemia	6 (6%)	9 (7%)	12 (6%)
Hyponatraemia	7 (8%)	7 (5%)	12 (6%)
Nasopharyngitis	11 (12%)	11 (8%)	12 (6%)
Oropharyngeal pain	3 (3%)	6 (4%)	12 (6%)
Weight decreased	7 (8%)	8 (6%)	12 (6%)
Dysphagia	6 (6%)	7 (5%)	11 (5%)
Hyperglycaemia	4 (4%)	7 (5%)	11 (5%)
Hyperkalaemia	6 (6%)	8 (6%)	11 (5%)
Influenza like illness	5 (5%)	6 (4%)	11 (5%)
Muscle spasms	8 (9%)	11 (8%)	11 (5%)
Rash maculo-papular	8 (9%)	9 (7%)	11 (5%)
Abdominal pain upper	8 (9%)	8 (6%)	10 (5%)
Chills	3 (3%)	4 (3%)	10 (5%)
Dehydration	4 (4%)	4 (3%)	10 (5%)
Pain	6 (6%)	6 (4%)	10 (5%)
Disease progression	3 (3%)	3 (2%)	9 (4%)
Haematuria	6 (6%)	6 (4%)	9 (4%)
Hypoxia	2 (2%)	3 (2%)	9 (4%)
Productive cough	6 (6%)	7 (5%)	9 (4%)
Proteinuria	3 (3%)	4 (3%)	9 (4%)
Sinus tachycardia	3 (3%)	4 (3%)	9 (4%)
Blood cholesterol increased	5 (5%)	6 (4%)	8 (4%)
Dyspepsia	2 (2%)	5 (4%)	8 (4%)
Hyperhidrosis	5 (5%)	7 (5%)	8 (4%)
Memory impairment	2 (2%)	2 (1%)	8 (4%)
Neuropathy peripheral	6 (6%)	6 (4%)	8 (4%)
Vision blurred	7 (8%)	8 (6%)	8 (4%)
Depression	4 (4%)	6 (4%)	7 (3%)
Dermatitis diaper	6 (6%)	7 (5%)	7 (3%)
Disturbance in attention	3 (3%)	5 (4%)	7 (3%)
Dysphonia	4 (4%)	5 (4%)	7 (3%)
Gastroenteritis	7 (8%)	7 (5%)	7 (3%)

Patients are counted once within each preferred term. Page 4
Reported adverse event terms were coded using MedDRA dictionary (version 18.1).
Adverse events are sorted in decreasing order of frequency based on the Overall Safety Analysis Set.
Percentages are calculated based on the number of patients in the column heading as the denominator.

In terms of TEAEs by Preferred Term (PT), most commonly reported in the Overall safety set were Fatigue (36 %), Dizziness (29 %), Nausea (28 %), Constipation (27 %), ALT increase, Anaemia, AST increase and Cough (26 % each), Vomiting (24 %9, Diarrhoea (23 %) and Pyrexia (18 %).

Similar proportions and patterns were observed in the Overall NTRK Fusion Cancers Safety set.

Table 82. TEAEs by Preferred Term and Maximum Severity (Larotrectinib Analysis Sets) as of cut-off date 30 July 2018, abbreviated, Overall Safety (N=208)

	Maximum Severity											
Preferred Term	Missing		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
Maximum Severity Grade	0	0%	31	15%	65	31%	82	39%	13	6%	12	6%	203	98%
Fatigue	0	0%	37	18%	31	15%	6	3%	0	0%	0	0%	74	36%
Dizziness	0	0%	52	25%	7	3%	2	1%	0	0%	0	0%	61	29%
Nausea	0	0%	50	24%	7	3%	2	1%	0	0%	0	0%	59	28%
Constipation	0	0%	45	22%	10	5%	1	0%	0	0%	0	0%	56	27%
Alanine aminotransferase increased	0	0%	37	18%	11	5%	6	3%	1	0%	0	0%	55	26%
Anaemia	0	0%	20	10%	15	7%	20	10%	0	0%	0	0%	55	26%
Aspartate aminotransferase increased	0	0%	38	18%	11	5%	6	3%	0	0%	0	0%	55	26%
Cough	0	0%	47	23%	6	3%	1	0%	0	0%	0	0%	54	26%
Vomiting	0	0%	36	17%	12	6%	1	0%	0	0%	0	0%	49	24%
Diarrhoea	0	0%	33	16%	12	6%	3	1%	0	0%	0	0%	48	23%
Pyrexia	0	0%	25	12%	11	5%	1	0%	1	0%	0	0%	38	18%
Dyspnoea	0	0%	20	10%	12	6%	5	2%	0	0%	0	0%	37	18%
Headache	0	0%	27	13%	8	4%	0	0%	0	0%	0	0%	35	17%
Myalgia	0	0%	24	12%	8	4%	2	1%	0	0%	0	0%	34	16%
Oedema peripheral	0	0%	25	12%	8	4%	0	0%	0	0%	0	0%	33	16%
Weight increased	0	0%	13	6%	10	5%	7	3%	0	0%	0	0%	30	14%
Arthralgia	0	0%	23	11%	5	2%	1	0%	0	0%	0	0%	29	14%
Abdominal pain	0	0%	19	9%	5	2%	3	1%	0	0%	0	0%	27	13%
Decreased appetite	0	0%	18	9%	5	2%	4	2%	0	0%	0	0%	27	13%
Pain in extremity	0	0%	17	8%	8	4%	2	1%	0	0%	0	0%	27	13%
Muscular weakness	0	0%	16	8%	10	5%	0	0%	0	0%	0	0%	26	13%
Back pain	0	0%	13	6%	11	5%	1	0%	0	0%	0	0%	25	12%
Nasal congestion	0	0%	24	12%	1	0%	0	0%	0	0%	0	0%	25	12%
Neutrophil count decreased	0	0%	5	2%	9	4%	9	4%	2	1%	0	0%	25	12%
Blood creatinine increased	0	0%	13	6%	8	4%	1	0%	0	0%	0	0%	22	11%
Leukocyte count decreased	0	0%	17	8%	3	1%	2	1%	0	0%	0	0%	22	11%
Hypertension	0	0%	8	4%	10	5%	3	1%	0	0%	0	0%	21	10%
Lymphocyte count decreased	0	0%	6	3%	8	4%	6	3%	1	0%	0	0%	21	10%
Upper respiratory tract infection	0	0%	4	2%	17	8%	0	0%	0	0%	0	0%	21	10%
Urinary tract infection	0	0%	2	1%	16	8%	3	1%	0	0%	0	0%	21	10%
Hypoalbuminaemia	0	0%	13	6%	5	2%	2	1%	0	0%	0	0%	20	10%
Dysgeusia	0	0%	18	9%	0	0%	0	0%	0	0%	0	0%	18	9%
Fall	0	0%	9	4%	7	3%	1	0%	0	0%	0	0%	18	9%
Blood alkaline phosphatase increased	0	0%	10	5%	6	3%	1	0%	0	0%	0	0%	17	8%
Hypokalaemia	0	0%	6	3%	3	1%	6	3%	1	0%	0	0%	16	8%
Dry skin	0	0%	14	7%	1	0%	0	0%	0	0%	0	0%	15	7%
Paraesthesia	0	0%	11	5%	2	1%	2	1%	0	0%	0	0%	15	7%
Hypotension	0	0%	9	4%	5	2%	0	0%	0	0%	0	0%	14	7%
Rash	0	0%	13	6%	1	0%	0	0%	0	0%	0	0%	14	7%
Abdominal distension	0	0%	13	6%	0	0%	0	0%	0	0%	0	0%	13	6%
Anxiety	0	0%	9	4%	4	2%	0	0%	0	0%	0	0%	13	6%
Asthenia	0	0%	10	5%	2	1%	1	0%	0	0%	0	0%	13	6%
Gait disturbance	0	0%	7	3%	4	2%	2	1%	0	0%	0	0%	13	6%
Hot flush	0	0%	13	6%	0	0%	0	0%	0	0%	0	0%	13	6%
Hypophosphataemia	0	0%	2	1%	3	1%	8	4%	0	0%	0	0%	13	6%
Insomnia	0	0%	8	4%	5	2%	0	0%	0	0%	0	0%	13	6%
Peripheral sensory neuropathy	0	0%	7	3%	5	2%	1	0%	0	0%	0	0%	13	6%
Platelet count decreased	0	0%	13	6%	0	0%	0	0%	0	0%	0	0%	13	6%

Continued,

Pruritus	0	0%	11	5%	2	1%	0	0%	0	0%	0	0%	13	6%
Flatulence	0	0%	10	5%	2	1%	0	0%	0	0%	0	0%	12	6%
Hypocalcaemia	0	0%	7	3%	2	1%	3	1%	0	0%	0	0%	12	6%
Hyponatraemia	0	0%	7	3%	0	0%	4	2%	1	0%	0	0%	12	6%
Nasopharyngitis	0	0%	8	4%	4	2%	0	0%	0	0%	0	0%	12	6%
Oropharyngeal pain	0	0%	11	5%	1	0%	0	0%	0	0%	0	0%	12	6%
Weight decreased	0	0%	8	4%	3	1%	1	0%	0	0%	0	0%	12	6%
Dysphagia	0	0%	7	3%	3	1%	1	0%	0	0%	0	0%	11	5%
Hyperglycaemia	0	0%	7	3%	2	1%	1	0%	1	0%	0	0%	11	5%
Hyperkalaemia	0	0%	5	2%	4	2%	2	1%	0	0%	0	0%	11	5%
Influenza like illness	0	0%	8	4%	3	1%	0	0%	0	0%	0	0%	11	5%
Muscle spasms	0	0%	8	4%	3	1%	0	0%	0	0%	0	0%	11	5%
Rash maculo-papular	0	0%	7	3%	3	1%	1	0%	0	0%	0	0%	11	5%
Abdominal pain upper	0	0%	8	4%	1	0%	1	0%	0	0%	0	0%	10	5%
Chills	0	0%	10	5%	0	0%	0	0%	0	0%	0	0%	10	5%
Dehydration	0	0%	1	0%	6	3%	3	1%	0	0%	0	0%	10	5%
Pain	0	0%	7	3%	3	1%	0	0%	0	0%	0	0%	10	5%
Disease progression	0	0%	0	0%	0	0%	1	0%	0	0%	8	4%	9	4%
Haematuria	0	0%	9	4%	0	0%	0	0%	0	0%	0	0%	9	4%
Hypoxia	0	0%	1	0%	7	3%	1	0%	0	0%	0	0%	9	4%
Productive cough	0	0%	8	4%	1	0%	0	0%	0	0%	0	0%	9	4%
Proteinuria	0	0%	7	3%	2	1%	0	0%	0	0%	0	0%	9	4%
Sinus tachycardia	0	0%	8	4%	1	0%	0	0%	0	0%	0	0%	9	4%
Blood cholesterol increased	0	0%	7	3%	1	0%	0	0%	0	0%	0	0%	8	4%
Dyspepsia	0	0%	7	3%	1	0%	0	0%	0	0%	0	0%	8	4%

Patients with multiple severity ratings for a given AE are counted once under the maximum severity. Page 40
Reported adverse event terms were coded using MedDRA dictionary (version 18.1).
Severity grade assignment based on CTCAE (v4.03): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), Grade 5 (fatal).

In the Overall safety set, Grade 3 were reported in 82 patients (39 %) and grade 4 in 13 patients (6%). The most common reported Grade 3 event was anaemia (10 %) and the remaining reports were isolated cases without any distinguishable pattern. The same is observed in terms of Grade 4 events. The corresponding proportions for the Efficacy-eval NTRK Fusion cancer set (N=93) is similar. A total of 40 reports (43 %) of Grade 3 and 8 cases (9 %) of Grade 4 with the most common Grade 3 event being also anaemia (10 %). In the Overall NTRK Fusion Cancers Safety (N=137), Grade 3 events were reported in 36 % and Grade 4 in 7 %.

Adult population

Table 83. Treatment-emergent Adverse Events by Recommended Dose for Adults (Subgroup Overall Safety Set, N=152) as of cut-off date 30 July 2018, abbreviated

Preferred Term	Recommended Dose (N=125)	All (N=152)
Patients with TEAE	122 (98%)	149 (98%)
Fatigue	47 (38%)	61 (40%)
Dizziness	46 (37%)	55 (36%)
Nausea	38 (30%)	44 (29%)
Anaemia	33 (26%)	42 (28%)
Constipation	31 (25%)	39 (26%)
Aspartate aminotransferase increased	29 (23%)	33 (22%)
Cough	29 (23%)	36 (24%)
Alanine aminotransferase increased	28 (22%)	31 (20%)
Myalgia	28 (22%)	29 (19%)
Diarrhoea	25 (20%)	29 (19%)
Dyspnoea	25 (20%)	33 (22%)
Oedema peripheral	25 (20%)	31 (20%)
Headache	22 (18%)	23 (15%)
Vomiting	21 (17%)	26 (17%)
Arthralgia	20 (16%)	22 (14%)
Back pain	19 (15%)	20 (13%)
Muscular weakness	18 (14%)	20 (13%)
Pyrexia	18 (14%)	21 (14%)
Weight increased	18 (14%)	20 (13%)
Dysgeusia	16 (13%)	17 (11%)
Urinary tract infection	15 (12%)	15 (10%)
Abdominal pain	14 (11%)	18 (12%)
Lymphocyte count decreased	14 (11%)	15 (10%)
Pain in extremity	14 (11%)	15 (10%)
Decreased appetite	13 (10%)	20 (13%)
Paraesthesia	13 (10%)	13 (9%)
Blood creatinine increased	12 (10%)	13 (9%)
Fall	12 (10%)	13 (9%)
Hypokalaemia	12 (10%)	14 (9%)
Peripheral sensory neuropathy	12 (10%)	12 (8%)
Upper respiratory tract infection	11 (9%)	11 (7%)
Abdominal distension	10 (8%)	11 (7%)
Hot flush	10 (8%)	12 (8%)
Hypertension	10 (8%)	12 (8%)
Nasal congestion	10 (8%)	13 (9%)
Weight decreased	10 (8%)	11 (7%)
Gait disturbance	9 (7%)	9 (6%)
Hypoalbuminaemia	9 (7%)	11 (7%)
Hyponatraemia	9 (7%)	10 (7%)
Hypophosphataemia	9 (7%)	11 (7%)
Chills	8 (6%)	10 (7%)
Dysphagia	8 (6%)	10 (7%)
Hypocalcaemia	8 (6%)	8 (5%)
Leukocyte count decreased	8 (6%)	8 (5%)
Muscle spasms	8 (6%)	9 (6%)
Pruritus	8 (6%)	8 (5%)

Patients are counted once within each preferred term. Page 2
Reported adverse event terms were coded using MedDRA dictionary (version 18.1).
Percentages are calculated based on the number of patients in the column heading as the denominator.
Recommended dose for adults (18 years or older): 100 mg BID.

In the subgroup of adults treated with the recommended dose in the Overall Safety Set (N=152), 98 % had any TEAEs with Fatigue (38 %), Dizziness (37 %), Nausea (30 %) and Anaemia (26 %) the most commonly events reported. AST and ALT elevations were reported in 23 % and 22 % respectively.

The corresponding proportion for the subgroup of adults treated with the recommended dose in the Overall NTRK Fusion Cancers Safety Set (N=90) shows a similar pattern with Dizziness (41 %) followed by Fatigue (38 %), Nausea (30 %) and Anaemia (24 %). AST and ALT elevations were reported in 26 % and 27 % respectively (Table not shown).

Paediatric population

Table 84. TEAEs by Recommended Dose for Paediatrics (Subgroup Overall Safety Set, N=56) as of cut-off date 30 July 2018, abbreviated

Preferred Term	Recommended Dose (N=42)	All (N=56)
Patients with TEAE	41 (98%)	54 (96%)
Alanine aminotransferase increased	16 (38%)	24 (43%)
Aspartate aminotransferase increased	15 (36%)	22 (39%)
Vomiting	15 (36%)	23 (41%)
Neutrophil count decreased	13 (31%)	18 (32%)
Constipation	12 (29%)	17 (30%)
Diarrhoea	12 (29%)	19 (34%)
Cough	11 (26%)	18 (32%)
Pyrexia	11 (26%)	17 (30%)
Anaemia	10 (24%)	13 (23%)
Fatigue	9 (21%)	13 (23%)
Headache	9 (21%)	12 (21%)
Leukocyte count decreased	9 (21%)	14 (25%)
Nausea	9 (21%)	15 (27%)
Pain in extremity	8 (19%)	12 (21%)
Platelet count decreased	7 (17%)	10 (18%)
Arthralgia	6 (14%)	7 (13%)
Hypoalbuminaemia	6 (14%)	9 (16%)
Nasal congestion	6 (14%)	12 (21%)
Upper respiratory tract infection	6 (14%)	10 (18%)
Abdominal pain	5 (12%)	9 (16%)
Blood alkaline phosphatase increased	5 (12%)	8 (14%)
Blood creatinine increased	5 (12%)	9 (16%)
Hyperglycaemia	5 (12%)	7 (13%)
Hypertension	5 (12%)	9 (16%)
Hypotension	5 (12%)	7 (13%)
Lymphocyte count decreased	5 (12%)	6 (11%)
Nasopharyngitis	5 (12%)	5 (9%)
Pruritus	5 (12%)	5 (9%)
Asthenia	4 (10%)	5 (9%)
Decreased appetite	4 (10%)	7 (13%)
Dermatitis diaper	4 (10%)	7 (13%)
Dizziness	4 (10%)	6 (11%)
Dry skin	4 (10%)	7 (13%)
Dyspnoea	4 (10%)	4 (7%)
Hypermagnesaemia	4 (10%)	4 (7%)
Irritability	4 (10%)	6 (11%)
Lymphocyte count increased	4 (10%)	4 (7%)
Rhinitis allergic	4 (10%)	6 (11%)
Sinus tachycardia	4 (10%)	6 (11%)
Weight increased	4 (10%)	10 (18%)
Abdominal pain upper	3 (7%)	4 (7%)
Conjunctivitis	3 (7%)	3 (5%)
Dysarthria	3 (7%)	4 (7%)
Flatulence	3 (7%)	5 (9%)
Haematuria	3 (7%)	6 (11%)
Hyperhidrosis	3 (7%)	4 (7%)

Continued,

Preferred Term	Recommended Dose (N=42)	All (N=56)
Hyperkalaemia	3 (7%)	6 (11%)
Musculoskeletal chest pain	3 (7%)	3 (5%)
Myalgia	3 (7%)	5 (9%)
Oropharyngeal pain	3 (7%)	6 (11%)
Proteinuria	3 (7%)	4 (7%)
Rash	3 (7%)	7 (13%)
Rhinitis	3 (7%)	4 (7%)
Back pain	2 (5%)	5 (9%)
Breath sounds abnormal	2 (5%)	3 (5%)
Contusion	2 (5%)	3 (5%)
Dehydration	2 (5%)	2 (4%)
Device related infection	2 (5%)	2 (4%)
Disturbance in attention	2 (5%)	2 (4%)
Drooling	2 (5%)	2 (4%)
Erythema	2 (5%)	4 (7%)
Eye pain	2 (5%)	2 (4%)
Fall	2 (5%)	5 (9%)
Gastroenteritis	2 (5%)	4 (7%)
Hemiparesis	2 (5%)	2 (4%)
Hypernatraemia	2 (5%)	3 (5%)
Hypocalcaemia	2 (5%)	4 (7%)
Hypokalaemia	2 (5%)	2 (4%)
Hypoxia	2 (5%)	2 (4%)
Influenza like illness	2 (5%)	3 (5%)

Patients are counted once within each preferred term. Page 3
Reported adverse event terms were coded using MedDRA dictionary (version 18.1).
Percentages are calculated based on the number of patients in the column heading as the denominator.
Recommended dose for pediatrics (<18 years): 100 mg/sq meter BID, not to exceed 100 mg BID.

In terms of the paediatric population, the pattern of reported events differs from that of the adult population. In the subgroup of paediatric patients treated with the recommended dose in the Overall Safety Set (N=56), 98 % had any TEAEs with ALT and AST elevations most commonly reported (38 % and 36 % respectively, followed by Vomiting (36 %), Neutrophil decreased (31 %), Constipation (29 %) and Diarrhoea (29 %).

The corresponding proportions for the subgroup of paediatric patients treated with the recommended dose in the Overall NTRK Fusion Cancers Safety Set (N=47), is very similar to that of the Overall safety Set with ALT and AST elevations most commonly reported (41 % and 35 % respectively, followed by Vomiting (35 %), Diarrhoea (32 %), Neutrophil decreased (30 %), and Constipation (30 %) (Table not shown).

Paediatric population by age cohorts

Note: Paediatric age group according to ICH E11 → Infants & Toddlers (28 days to 23 months), Children (2 to 11 years), Adolescents (12 to <18 years).

Table 85: TEAEs by Paediatric Age Group (Paediatric Subgroup Overall Safety Set, N=56), abbreviated

Preferred Term	Infants & Toddlers (N=18)	Children (N=23)	Adolescents (N=15)
Patients with TEAE	17 (94%)	22 (96%)	15 (100%)
Alanine aminotransferase increased	11 (61%)	9 (39%)	4 (27%)
Aspartate aminotransferase increased	8 (44%)	9 (39%)	5 (33%)
Vomiting	11 (61%)	8 (35%)	4 (27%)
Abdominal pain	0 (0%)	7 (30%)	2 (13%)
Cough	8 (44%)	7 (30%)	3 (20%)
Diarrhoea	11 (61%)	7 (30%)	1 (7%)
Headache	0 (0%)	7 (30%)	5 (33%)
Pyrexia	10 (56%)	6 (26%)	1 (7%)
Constipation	10 (56%)	5 (22%)	2 (13%)
Nasal congestion	5 (28%)	5 (22%)	2 (13%)
Pain in extremity	1 (6%)	5 (22%)	6 (40%)
Abdominal pain upper	0 (0%)	4 (17%)	0 (0%)
Anaemia	8 (44%)	4 (17%)	1 (7%)
Arthralgia	0 (0%)	4 (17%)	3 (20%)
Blood alkaline phosphatase increased	2 (11%)	4 (17%)	2 (13%)
Fatigue	7 (39%)	4 (17%)	2 (13%)
Leukocyte count decreased	5 (28%)	4 (17%)	5 (33%)
Nausea	6 (33%)	4 (17%)	5 (33%)
Neutrophil count decreased	9 (50%)	4 (17%)	5 (33%)
Pruritus	1 (6%)	4 (17%)	0 (0%)
Rhinitis	0 (0%)	4 (17%)	0 (0%)
Weight increased	4 (22%)	4 (17%)	2 (13%)
Agitation	1 (6%)	3 (13%)	0 (0%)
Back pain	0 (0%)	3 (13%)	2 (13%)
Blood creatinine increased	3 (17%)	3 (13%)	3 (20%)
Decreased appetite	3 (17%)	3 (13%)	1 (7%)
Dry skin	3 (17%)	3 (13%)	1 (7%)
Hyperhidrosis	1 (6%)	3 (13%)	0 (0%)
Hypertension	3 (17%)	3 (13%)	3 (20%)
Hypoalbuminaemia	5 (28%)	3 (13%)	1 (7%)
Irritability	2 (11%)	3 (13%)	1 (7%)
Muscular weakness	0 (0%)	3 (13%)	3 (20%)
Nasopharyngitis	1 (6%)	3 (13%)	1 (7%)
Platelet count decreased	5 (28%)	3 (13%)	2 (13%)
Rash	4 (22%)	3 (13%)	0 (0%)
Upper respiratory tract infection	6 (33%)	3 (13%)	1 (7%)
Urinary tract infection	3 (17%)	3 (13%)	0 (0%)
Asthenia	2 (11%)	2 (9%)	1 (7%)
Dizziness	0 (0%)	2 (9%)	4 (27%)
Dysarthria	0 (0%)	2 (9%)	2 (13%)
Eye pain	0 (0%)	2 (9%)	0 (0%)
Gait disturbance	1 (6%)	2 (9%)	1 (7%)
Gastroenteritis	2 (11%)	2 (9%)	0 (0%)
Hyperkalaemia	3 (17%)	2 (9%)	1 (7%)

Patients are counted once within each preferred term. Page 2
Reported adverse event terms were coded using MedDRA dictionary (version 18.1).
Percentages are calculated based on the number of patients in the column heading as the denominator.
Pediatric age group according to ICH E11. Infants & Toddlers (28 days to 23 months), Children (2 to 11 years), Adolescents (12 to <18 years).

Continued,

Preferred Term	Infants & Toddlers (N=18)	Children (N=23)	Adolescents (N=15)
Hypernatraemia	1 (6%)	2 (9%)	0 (0%)
Hypotension	4 (22%)	2 (9%)	1 (7%)
Influenza	1 (6%)	2 (9%)	0 (0%)
Laceration	0 (0%)	2 (9%)	0 (0%)
Myalgia	0 (0%)	2 (9%)	3 (20%)
Oropharyngeal pain	1 (6%)	2 (9%)	3 (20%)
Pollakiuria	0 (0%)	2 (9%)	0 (0%)
Productive cough	1 (6%)	2 (9%)	0 (0%)
Rash pruritic	0 (0%)	2 (9%)	0 (0%)
Urinary tract pain	0 (0%)	2 (9%)	0 (0%)
Urticaria	0 (0%)	2 (9%)	0 (0%)
Viral upper respiratory tract infection	0 (0%)	2 (9%)	0 (0%)
Abdominal distension	1 (6%)	1 (4%)	0 (0%)
Alopecia	0 (0%)	1 (4%)	0 (0%)
Animal bite	0 (0%)	1 (4%)	0 (0%)
Anxiety	1 (6%)	1 (4%)	0 (0%)
Bacterial vaginosis	0 (0%)	1 (4%)	0 (0%)
Blood albumin decreased	0 (0%)	1 (4%)	0 (0%)
Blood lactate dehydrogenase increased	0 (0%)	1 (4%)	1 (7%)
Bone pain	0 (0%)	1 (4%)	0 (0%)
Bronchial obstruction	0 (0%)	1 (4%)	0 (0%)
Bronchitis	0 (0%)	1 (4%)	0 (0%)
Cardiac murmur	0 (0%)	1 (4%)	0 (0%)
Chalazion	0 (0%)	1 (4%)	0 (0%)
Conjunctival hyperaemia	0 (0%)	1 (4%)	0 (0%)
Conjunctivitis	1 (6%)	1 (4%)	1 (7%)
Croup infectious	0 (0%)	1 (4%)	0 (0%)
Dermatitis contact	1 (6%)	1 (4%)	0 (0%)
Dermatitis diaper	6 (33%)	1 (4%)	0 (0%)
Drooling	1 (6%)	1 (4%)	0 (0%)
Dysgeusia	0 (0%)	1 (4%)	0 (0%)
Dyskinesia	0 (0%)	1 (4%)	0 (0%)
Dysphagia	0 (0%)	1 (4%)	0 (0%)
Dysphonia	0 (0%)	1 (4%)	0 (0%)
Dyspnoea	1 (6%)	1 (4%)	2 (13%)
Dyspnoea exertional	0 (0%)	1 (4%)	0 (0%)
Dysuria	0 (0%)	1 (4%)	0 (0%)
Ear pain	0 (0%)	1 (4%)	0 (0%)
Electrocardiogram QT prolonged	0 (0%)	1 (4%)	0 (0%)
Enterocolitis	0 (0%)	1 (4%)	0 (0%)
Epistaxis	0 (0%)	1 (4%)	0 (0%)
Erythema	3 (17%)	1 (4%)	0 (0%)
Eyelid ptosis	0 (0%)	1 (4%)	0 (0%)
Facial nerve disorder	0 (0%)	1 (4%)	0 (0%)
Facial pain	0 (0%)	1 (4%)	0 (0%)
Fall	2 (11%)	1 (4%)	2 (13%)

Patients are counted once within each preferred term. Page 4
Reported adverse event terms were coded using MedDRA dictionary (version 18.1).
Percentages are calculated based on the number of patients in the column heading as the denominator.
Pediatric age group according to ICH E11. Infants & Toddlers (28 days to 23 months), Children (2 to 11 years), Adolescents (12 to <18 years).

In the youngest age-group (Infants and Toddlers, N=18), 94 % had any TEAEs with ALT elevations, Vomiting and Diarrhoea (61 % each) most commonly reported followed by Pyrexia and Constipation (56 % each), Neutrophil count decreased (50 %), AST elevations, Cough and Anaemia (44 % each) and Fatigue (39 %).

For the Children age group (N=23), the corresponding proportions are 96 % with any TEAE and most commonly reported are AST and ALT elevations (39 %) each, Vomiting (35 %), Cough, Diarrhoea and headache (30 % each).

In terms of Adolescents (N=15), all patients reported any TEAE with Pain in extremity most commonly reported (40 %), followed by AST elevation, Neutrophil count decreased, Nausea and Headache most commonly reported (33 %) ALT elevation, Vomiting and Dizziness (27 % each).

The limited number of patients in each paediatric age cohort is recognised thus hampering any firm conclusions. Nevertheless, in the youngest age cohort there were more TEAEs reported in terms of e.g. neutropenia, anaemia, pyrexia, GI disorders (diarrhoea, vomiting, constipation and nausea) and weight increase as compared to the older age cohorts.

In terms of the Overall NTRK Fusion Cancers Safety Set (N=47), with a total of 18 patients enrolled in the age group of Infants and Toddlers, 20 patients in the Children age group and 9 patients in the Adolescents group, the pattern and proportions of reported PTs are similar to that of the Paediatric Subgroup Overall Safety Set above (Table not shown).

Adverse drug reactions (ADRs)

Since all the safety data for the ADR assessments were from open-label Phase 1 and Phase 2 studies (with no comparator arm), the determination of ADRs was primarily based on investigators' causality assessments of reported events:

- AEs were assessed as ADRs if half or more (≥ 50%) of these were regarded as at least possibly drug related by investigators (based on company internal guideline for generating ADRs).

- Plausible pharmacological effect based on larotrectinib mode of action, clinical relevance, frequency and severity were taken into consideration in the determination of ADRs.

Frequency of ADRs identified was determined on the basis of the total number of patients treated with larotrectinib (n=208). This was used as a denominator for frequency determination of these ADRs. As of the data cut-off date 30 July 2018, there were three on-going studies (Studies 1, 2 ("NAVIGATE"), and 3 ("SCOUT")), and no available postmarketing data.

- For all ADRs identified, frequency was determined irrespective of investigator's causality assessment.

- The threshold of ≥ 5% was applied for selection of the ADRs from the Common Related AEs.

Table 86: Adverse drug reactions reported in NTRK fusion positive patients treated with VITRAKVI at recommended dose (n=125)

System Organ Class Adverse Drug Reaction	VITRAKVI N = 125 All Grades n (%)	 Grade 3-4 n (%)
Blood and Lymphatic Disorders System Disorders		
Anaemia	30 (24)	9 (7)
Leukocyte count decreased	16 (13)	2 (2)
Neutrophil count decreased	17 (14)	7 (6)
Nervous System Disorders		
Dizziness	38 (30)	1 (1)
Gait Disturbance	4 (3)	0 (0)
Paraesthesia	12 (10)	2 (2)
Gastrointestinal Disorders		
Constipation	36 (29)	0 (0)
Dysgeusia	11 (9)	0 (0)
Nausea	33 (26)	1 (1)
Vomiting	25 (20)	0 (0)
Musculoskeletal and Connective Tissue Disorders		
Muscular weakness	13 (10)	0 (0)
Myalgia	22 (18)	1 (1)
General Disorders and Administrative Site Conditions		
Fatigue	40 (32)	1 (1)
Investigations		
Blood alkaline phosphatase increased	7 (6)	0 (0)
Alanine aminotransferase increased	39 (31)	4 (3)
Aspartate aminotransferase increased	36 (29)	2 (2)
Weight increased	20 (16)	3 (2)

Reported adverse event terms were coded using MedDRA dictionary (version 18.1) and graded according to CTCAE version 4.03.
Source: TEAEs in overall NTRK fusion positive cancers (data cut-off 30 JUL 2018) and TEAEs by age group (cut-off 30 JUL 2018).

Of 125 patients treated with larotrectinib in the overall NTRK fusion safety population at the recommended dose, 37 (30%) patients were from 28 days to 18 years of age. Of these 37 patients, 38% were 28 days to < 2 years (n=14), 41% were 2 years to < 12 years (n=15), and 22% were 12 years to < 18 years (n=8).

The majority of adverse reactions were Grade 1 or 2 in severity and were resolved without larotrectinib dose modification or discontinuation. The adverse reactions of vomiting (35% versus 14% in adults), leucocyte count decrease (22% versus 9% in adults), neutrophil count decrease (30% versus 7% in adults), blood alkaline phosphatase increased (14% versus 2% in adults) and transaminase elevations (ALT 41% versus 27% in adults and AST 35% versus 26% in adults) were more frequent in paediatric patients compared to adults.

Table 87: Adverse drug reactions reported in NTRK fusion positive paediatric patients treated with VITRAKVI at recommended dose (n=37); All Grades

System Organ Class Adverse Drug Reaction	Patient Incidence, n (%); N = 37 Infants and toddlers (n=14)[a]	Children (n=15)[b]	Adolescents (n=8)[c]	Total paediatric (n=37)
Blood and lymphatic system disorders				
Anaemia	6 (43)	3 (20)	0 (0)	9 (24)
Leukocyte count decreased	3 (21)	3 (20)	2 (25)	8 (22)
Neutrophil count decreased	6 (43)	3 (20)	2 (25)	11 (30)
Nervous System Disorders				
Dizziness	0 (0)	0 (0)	2 (25)	2 (5)
Gait disturbance	0 (0)	1 (7)	0 (0)	1 (3)
Paraesthesia	0 (0)	1 (7)	1 (13)	2 (5)
Gastrointestinal Disorders				
Constipation	8 (57)	3 (20)	0 (0)	11 (30)
Dysgeusia	0 (0)	1 (7)	0 (0)	1 (3)
Nausea	3 (21)	2 (13)	2 (25)	7 (19)
Vomiting	8 (57)	4 (27)	1 (13)	13 (35)
Musculoskeletal and Connective Tissue Disorders				
Muscular weakness	0 (0)	0 (0)	1 (13)	1 (3)
Myalgia	0 (0)	1 (7)	2 (25)	3 (8)
General Disorders and Administrative Site Conditions				
Fatigue	5 (36)	2 (13)	0 (0)	7 (19)
Investigations				
Blood alkaline phosphatase increased	1 (7)	3 (20)	1 (13)	5 (14)
Alanine aminotransferase increased	8 (57)	6 (40)	1 (13)	15 (41)
Aspartate aminotransferase increased	6 (43)	6 (40)	1 (13)	13 (35)
Weight increased	2 (14)	2 (13)	0 (0)	4 (11)

[a] Infants/toddlers: one Grade 4 Neutrophil count decreased (Neutropenia) event reported. Grade 3 events included two cases Neutrophil count decreased (Neutropenia) and one case of Anaemia.

[b] Children: No Grade 4 reactions were reported. One reported Grade 3 case each of Neutrophil count decreased (Neutropenia), Paraesthesia, Myalgia, Weight increased (Abnormal weight gain).

[c] Adolescents: No Grades 3 and 4 reactions were reported.

Reported adverse event terms were coded using MedDRA dictionary (version 18.1) and graded according to CTCAE version 4.03.

Source: TEAEs by paediatric age group (Table 14.4.26.2.1 and 14.4.26.2.2, data cut-off 30 JUL 2018)

Adverse Events of Special Interest (AESIs)

Note: The assessment of AESIs below is based on data with the data cut-off date of 19 February 2018

Based on predictions from the TRK-related neurobiology literature, the preclinical toxicology program, and clinical experience with larotrectinib, the following three AESIs were pre- identified:

Transaminase (ALT or AST) increases

Increases in ALT and/or AST were predicted off-target effects from the preclinical toxicology program.

In the overall NTRK fusion safety database (n=125), the maximum grade transaminase elevation observed was Grade 4 ALT increase in 1 patient (<1%). Grade 3 ALT and AST increases in 3 (2%) and 2

(2%) patients, respectively. Majority of Grade 3 elevations were transient appearing in first or second month of treatment and resolving to Grade 1 by months 3-4. Grade 2 ALT and AST increases were observed in 9 (7%) and 6 (5%) of patients, respectively, and Grade 1 ALT and AST increases were observed in 26 (21%) and 28 (22%) of patients, respectively. ALT and AST increases leading to dose modifications occurred in 7 (6%) patients and 6 (5%) patients, respectively. No patient permanently discontinued the treatment due to Grade 3 4 ALT and AST increases (see sections 4.4 and 4.8 of the SmPC).

No cases of Hy's Law of drug induced liver injury have been confirmed.

The incidence of ALT increased and AST increased was higher in paediatric patients compared with adult patients. The incidence of ALT increased was 58% in infants and toddlers compared with 42% in children and 31% in adolescents, and the incidence of AST increased was 42% in infants and toddlers compared with 37% in children and 38% in adolescents.

There are no indications of any cumulative hepatic toxicity in terms of ALT/ AST increases by larotrectinib.

The Applicant proposes to include "Severe drug-induced liver injury" as an Important Potential Risk in the safety specification which is supported.

Neutropenia

Neutropenia was not seen in preclinical studies but was observed in clinical trials, mainly in paediatric patients and most commonly in the youngest paediatric age cohorts. At the data cut-off 30 July 2018, neutropenia has been reported in 25 patients (12%). 72% of neutropenia occurred in paediatric population (Grade 1 in 3 patients, Grade 2 in 7 patients, Grade 3 in 7 patients and Grade 4 in 1 patient).

A total of 11 cases of neutropenia reported in paediatric population were considered to be related to larotrectinib (2 Grade 1, 6 Grade 2, 2 Grade 3 and 1 Grade 4). No treatment discontinuation was required due to neutropenia. One febrile neutropenia has been reported in a 16-months old patient but considered as not treatment related.

Investigators reported neutropenia as a TEAE (PT neutrophil count decreased) in 17 (10%) patients and this was considered by the investigator to be related to treatment in 9 (5%) patients. In addition, an SAE of febrile neutropenia was reported for 1 patient (considered unrelated to study drug). Fifteen of the 18 observations were observed in paediatric patients. Worst severity was Grade 1 in 4 patients, Grade 2 in 5 patients, Grade 3 in 8 patients (including the case of febrile neutropenia), and Grade 4 in 1 patient. Neutropenia leading to dose modification occurred in 4 patients and to dose reduction in two patients. None led to treatment discontinuation.

Changes in neutrophil counts using laboratory reports for all patients included in the Overall safety analysis set were analysed. As is observed with the investigator reported TEAEs for neutropenia, most were Grade 1 or 2, and 33 of 39 (85%) reports occurred within the first 3 cycles (one cycle is defined as 28 days) of larotrectinib treatment.

The Applicant is committed to continue to monitor neutropenia both in adult and paediatric patients. Infections secondary to neutropenia has been added as important potential risk in the RMP.

Neurologic effects

There is potential for on-target central effects of larotrectinib in humans (neurologic reactions) due to the mechanism of action (neurotrophin signaling). In the postnatal period, TRK receptors are expressed in the brain and nervous system and are thought to regulate mood, memory, cognition, and proprioception.

In the overall NTRK fusion safety database (n=125), the maximum grade neurologic reaction observed was Grade 3 which was observed in three (2%) patients and included dizziness (one patient, <1%) and

paraesthesia (two patients, 1.6%). The overall incidence was 30% for dizziness, 10% for paraesthesia and 3% for gait disturbance. Neurologic reactions leading to dose modification included dizziness (2%). None of these adverse reactions led to treatment discontinuation. In all cases, patients with evidence of anti-tumour activity who required a dose reduction were able to continue dosing at a reduced dose and/or schedule

The incidence of the five most commonly reported neurologic events regardless of severity (dizziness, gait disturbance, paraesthesia, anxiety, and peripheral sensory neuropathy) was lower in paediatric patients compared with adult patients with the exception of gait disturbance.

The time to onset of the first episode was generally within the first month of starting treatment. For most patients no action with study drug was required. The majority of episodes resolved without sequelae and 16 of these TEAEs were ongoing as of the data cut-off.

There were 15 patients with primary or metastatic brain tumours included in the clinical studies. Neurologic TEAEs were reported by 10 of these patients: the TEAEs reported were dizziness (2 patients), vertigo, (2 patients), dysarthria (2 patients), hypoaesthesia (2 patients), balance disorder, paraesthesia, sensory disturbance, agitation, gait disturbance, extrapyramidal disorder, neuralgia, peripheral sensory neuropathy, cognitive disorder, memory impairment, mental status changes, delirium, dyskinesia (each 1 patient). Two were considered by the investigators to be related to study treatment.

Serious adverse event/deaths/other significant events

Serious Adverse Events

Table 88: Serious TEAEs (Larotrectinib Analysis Sets) as of Data Cut-off 30 Jul 2018, abbreviated

Preferred Term	Efficacy-eval NTRK Fusion Cancers (N=93)	Overall NTRK Fusion Cancers Safety (N=137)	Overall Safety (N=208)
Patients with TEAE	31 (33%)	38 (28%)	70 (34%)
Disease progression	3 (3%)	3 (2%)	9 (4%)
Pyrexia	5 (5%)	6 (4%)	7 (3%)
Diarrhoea	3 (3%)	4 (3%)	5 (2%)
Sepsis	4 (4%)	4 (3%)	4 (2%)
Abdominal pain	1 (1%)	1 (1%)	3 (1%)
Cellulitis	2 (2%)	2 (1%)	3 (1%)
Dehydration	1 (1%)	1 (1%)	3 (1%)
Dyspnoea	2 (2%)	2 (1%)	3 (1%)
Pneumonia	0 (0%)	1 (1%)	3 (1%)
Vomiting	1 (1%)	2 (1%)	3 (1%)
Alanine aminotransferase increased	2 (2%)	2 (1%)	2 (1%)
Anaemia	1 (1%)	2 (1%)	2 (1%)
Aspartate aminotransferase increased	2 (2%)	2 (1%)	2 (1%)
Bile duct obstruction	1 (1%)	1 (1%)	2 (1%)
Constipation	1 (1%)	1 (1%)	2 (1%)
Cough	2 (2%)	2 (1%)	2 (1%)
Device related infection	2 (2%)	2 (1%)	2 (1%)
Fatigue	1 (1%)	1 (1%)	2 (1%)
Gastroenteritis viral	2 (2%)	2 (1%)	2 (1%)
Hyponatraemia	1 (1%)	1 (1%)	2 (1%)
Influenza	2 (2%)	2 (1%)	2 (1%)
Metastases to central nervous system	0 (0%)	0 (0%)	2 (1%)
Muscular weakness	0 (0%)	0 (0%)	2 (1%)
Nausea	1 (1%)	1 (1%)	2 (1%)
Pleural effusion	0 (0%)	0 (0%)	2 (1%)
Pulmonary embolism	2 (2%)	2 (1%)	2 (1%)
Small intestinal obstruction	2 (2%)	2 (1%)	2 (1%)
Acetabulum fracture	0 (0%)	0 (0%)	1 (0%)
Acute kidney injury	0 (0%)	1 (1%)	1 (0%)
Acute myeloid leukaemia	0 (0%)	0 (0%)	1 (0%)
Ascites	1 (1%)	1 (1%)	1 (0%)
Ataxia	0 (0%)	0 (0%)	1 (0%)
Blood creatinine increased	0 (0%)	0 (0%)	1 (0%)
Bradycardia	0 (0%)	1 (1%)	1 (0%)
Brain oedema	0 (0%)	0 (0%)	1 (0%)
Bronchiolitis	1 (1%)	1 (1%)	1 (0%)
Cerebellar haemorrhage	0 (0%)	0 (0%)	1 (0%)
Cerebrovascular accident	1 (1%)	1 (1%)	1 (0%)
Decreased appetite	0 (0%)	0 (0%)	1 (0%)
Deep vein thrombosis	1 (1%)	1 (1%)	1 (0%)

Patients are counted once within each preferred term. Page 2
Reported adverse event terms were coded using MedDRA dictionary (version 18.1).
Adverse events are sorted in decreasing order of frequency based on the Overall Safety Analysis Set.
Percentages are calculated based on the number of patients in the column heading as the denominator.

A total of 34 % in the Overall Safety Analysis set experienced at least one SAE during treatment with similar results for the NTRK gene fusion analysis set (28 %) and the Efficacy-evaluable NTRK gene fusion analysis set (33 %). Most commonly reported in the Overall Safety Analysis set (aside from disease progression which is not regarded as an AE) was pyrexia (3 %), diarrhoea and sepsis (each reported in 2 %).

Deaths

Note, the assessment below is based on data with the data cut-off date of 19 February 2018

Table 89: Deaths Reported within 30 Days of Last Dose of Larotrectinib (Overall Safety Analysis Set)

Study	Patient	Age (years)	Primary Malignancy	Larotrectinib Starting Dose	Cause of Death/Fatal AE	Study Day of Death	Days from Last Dose	Relationship to Study Drug
Patients with TEAEs with a fatal outcome								
14001	[redacted]		Pancreas	100 mg BID	Disease progression	71	26	Not related
14001			Thymus	100 mg QD	Metastases to central nervous system	71	7	Not related
14001			Pancreas	200 mg QD	Disease progression	30	15	Not related
14001			Breast	100 mg BID	Disease progression	6	2	Not related
14001			Colon	200 mg BID	Disease progression	97	13	Not related
15002			Colorectal	100 mg BID	Intestinal perforation[a]	84	3	Not related
15002			Colorectal	100 mg BID	Small intestinal obstruction[b]	84	26	Not related
15002			Sarcoma	100 mg BID	Disease progression	36	17	Not related
15002			Biliary	100 mg BID	Disease progression	56	29	Not related
15003			Medulloblastoma	125 mg BID	Disease progression	46	2	Not related
15003			Astrocytoma	100 mg BID	Cerebellar haemorrhage[c]	12	1	Not related

Source: Module 5.3.5.3, CSS_19 FEB 2018, Listing 16.2.3.2; Study LOXO-TRK-14001 CSR, Section 14.3.3; Study LOXO-TRK-14001 CSR Addendum, Section 14.3; Study LOXO-TRK-15002 CSR, Section 14.3.3; Study LOXO-TRK 15002 CSR Addendum, Section 14.3.3; Study LOXO-TRK-15003 CSR, Section 14.4; Study LOXO-TRK-15003 CSR Addendum, Section 14.4.

Status as of 19 FEB 2018

[a] Patient noted to have Grade 5 intestinal perforation due to progressive disease

[b] Histology of the mass in the small intestine was similar to the original histology

[c] Hemorrhage of left cerebellar metastasis

[d] Not reported as an adverse event, therefore no relationship to larotrectinib was available.

Abbreviations: BID = twice daily; TEAE = treatment-emergent adverse event

In total 30 deaths have been reported at any time for the Overall Safety Analysis seta and 11 patients (6%) experienced TEAEs with a fatal outcome within 30 days of receiving larotrectinib (5 patients in study LOXO-TRK-14001, 4 in LOXO-TRK-15002 and 2 in LOXO-TRK-15003). All were attributed to either disease progression (7 patients) or to a complication of the primary malignancy. None of the cases were considered related to the investigational drug.

The reasons for deaths that occurred > 30 days after the last dose of study drug were disease progression (14 patients) and unknown cause (4 patients).

Laboratory findings

Note: the assessment below is based on data with the data cut-off date of 19 February 2018

Haematology

Anaemia was reported as a TEAE for 45 (26%) patients (19 [11%] considered treatment related). No patients were permanently discontinued due to TEAEs of anaemia, but 2 (1%) patients had a dose modification or interruption for this TEAE.

Based on shift analysis, no treatment emergent effects were seen in platelet counts.

Changes in neutrophil counts using laboratory reports for all patients included in the Overall safety analysis set were analysed. As is observed with the investigator reported TEAEs for neutropenia, most were Grade 1 or 2, and 33 of 39 (85%) reports occurred within the first 3 cycles (one cycle is defined as 28 days) of larotrectinib treatment.

Clinical Chemistry

At any time during the study (regardless of baseline value), the maximum grade reported for ALT elevations was Grade 1 for 76 (43 %) patients, Grade 2 for 12 (7 %) patients, and Grade 3 for 5 (3 %) patients. At the time of the data cut a Grade 4 TEAE of elevated ALT was reported for Patient [redacted]

however the corresponding raw laboratory data reported at that time equated to a Grade 3 ALT elevation. The correct corresponding laboratory value equating to a Grade 4 ALT has since been updated and will be reflected in future reports.

At any time during the study (regardless of baseline value), the maximum grade reported for AST elevations was Grade 1 for 79 (45%) patients, Grade 2 for 12 (7%) patients, and Grade 3 for 6 (3%) patients.

Grade 3 of bilirubin increase was reported in 3 % (6 patients). In terms of albumin decrease there were 6 reports of Grade 3 events (3 %, no Grade 4) and 4 reports of Grade 3 phosphorus decrease (2 %) with 1 report of Grade 4 in the Overall safety Analysis set.

Body Weight

Body weight changes are presented using a cut-off date of 17 July 2017. The majority of adult patients (62 %) showed no change in either the upward or downward direction.

Body weight changes in paediatric patients were assessed by summary statistics on the change in percentile from standard growth charts. Median percentile increased from a baseline of 30.4 % to a last value of 71.7 %. The median maximum decrease was 0.2 % and the median maximum increase was 8.5 %. In general, these changes represented both normal growth and development and normalization of low baseline body weights. However, 7 patients in LOXO TRK 15003 were reported with body weight increase as a TEAE. Weight increased was reported in 10 (23%) pediatric patients compared with 16 (12%) adult patients.

Electrocardiograms (ECG)

A clinical pharmacology study, LOXO-TRK-16009 (Phase 1 single ascending dose, randomized, double-blind, placebo-controlled study), was conducted in 36 subjects to evaluate doses of 100 to 900 mg for their impact on ECG parameters (please refer to the PK section).

In cancer patients treated with 100 mg BID larotrectinib, twice the "worst case" Cmax was considered to be approximately 5100 ng/mL and at this concentration, the modelled value for ddQTcF was -3.318 msec with 90% upper CI -2.127 msec. There were no QTcF values >450 msec observed at baseline or post treatment or change from baseline values greater than 30 msec on this study. No other ECG parameters reached the pre-specified out-of-normal range categories for PR, QRS, and heart rate.

Safety in special populations

Note: the assessment below is based on data with the data cut-off date of 19 February 2018

Gender

The percentage of patients with 1 or more AEs was very similar for males and females (99 % and 98 % respectively). Males had higher incidences (10% or greater relative to females) of dizziness (38% vs 18%), ALT increased (31% vs 20%), headache (19% vs 9%), and weight decreased (12% vs 0).

Race

The vast majority of patients included in the Overall Safety Analysis set were white (72 %).

Age

Table 90: Common AEs by Age Group (Occurring in≥ 20% of any Age Group) (Overall Safety Analysis Set)

	Patient incidence, n (%)		
	<18 years	≥18 years	≥65 years
N	44	132	38
Any TEAE	42 (95)	131 (99)	38 (100)
Fatigue	10 (23)	55 (42)	20 (53)
Dizziness	5 (11)	45 (34)	13 (34)
Nausea	15 (34)	36 (27)	10 (26)
Anaemia	10 (23)	35 (27)	15 (39)
Cough	16 (36)	30 (23)	7 (18)
Constipation	11 (25)	29 (22)	12 (32)
AST increased	17 (39)	28 (21)	7 (18)
Dypsnoea	3 (7)	28 (21)	10 (26)
ALT increased	19 (43)	26 (20)	7 (18)
Diarrhoea	13 (30)	26 (20)	7 (18)
Oedema peripheral	1 (2)	26 (20)	8 (21)
Vomiting	21 (48)	24 (18)	7 (18)
Pyrexia	12 (27)	19 (14)	6 (16)
Weight increased	10 (23)	16 (12)	1 (3)
Headache	10 (23)	15 (11)	4 (11)
Fall	5 (11)	12 (9)	8 (21)
Hypertension	9 (20)	10 (8)	4 (11)
Nasal congestion	9 (20)	9 (7)	1 (3)
Leukocyte count decreased	10 (23)	4 (3)	1 (3)
Neutrophil count decreased	14 (32)	3 (2)	1 (3)

Source: Module 5.3.5.3, ISS_19 FEB 2018, Table 14.4.26.1.1
Status as of 19 FEB 2018
Abbreviation: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event

The following TEAEs were reported ≥10% in patients <18 years than in patients ≥18 years: cough (36% vs 23%), AST increased (39% vs 21%), ALT increased (43% vs 20%), diarrhoea (30% vs 20%), vomiting (48% vs 18%), pyrexia (27% vs 14%), weight increased (23% vs 12%), headache (23% vs 11%), hypertension (20% vs 8%), nasal congestion (20% vs 7%), leukocyte count decreased (23% vs 3%) and neutrophil count decreased (32% vs 3%).

In the updated Overall Safety Dataset (data cut-off 30 July 2018), hypertension has been reported in 21 (10%) patients, 16% in paediatrics vs 8% in adults.

In paediatric patients, hypertension Grade 1 and Grade 2 were reported in 5 patients and 4 patients respectively. No Grade 3-4 has been reported. Hypertension has been considered as related to laroctectinib in three cases.

The following TEAEs were reported ≥10% in patients ≥18 years than in patients <18 years: fatigue (42% vs 23%), dizziness (34% vs 11%), dyspnoea (21% vs 7%) and oedema peripheral (20% vs 2%).

The following TEAEs were reported ≥10% in patients ≥65 years than in patients ≥18 years: fatigue (53% vs 42%), anaemia (39% vs 27%), constipation (32% v 22%) and fall (21% vs 9%). Only 9 patients ≥ 75 years old are included in the overall safety analysis set. Safety data are limited in this category of patient.

AEs adjudicated as related AEs was generally consistent across age group:

The most commonly reported related AE in the paediatric population were: ALT increased (36%), AST increased (32%), leukocytes count decreased (20%), neutrophil count decreased (20%), anaemia (16%), nausea (14%), fatigue (13%), constipation (13%) and vomiting 11%).

In the adult population they were: dizziness (28%), fatigue (20%), ALT increased (16%), nausea (16%), AST increased (15%), constipation (23%), myalgia (11%) and dysgueusia (10%).

The most commonly reported related AE in patients ≥ 65 year of age were: dizziness (30%), fatigue (28%), constipation (17%), ALT increased (15%), nausea (15%), AST increased (15%), vomiting (11%), anaemia (11%) and gait disturbance (11%).

Grade ≥ 3 related AEs are low in each treatment group with anaemia the most commonly reported in adult patients (12%) and in patients ≥ 65 years of age (23%), whilst for the paediatric patients it is neutrophil count decreased in (14%).

The median age in the Overall safety Population was 51 years.

Table 91: AEs in elderly populations (new cut-off date of 30 July 2018)

MedDRA Terms	**Age <65 number (percentage)** N=161 (100%)	**Age 65-74 number (percentage)** N=36 (100%)	**Age 75-84 number (percentage)** N=11 (100%)	**Age 85+ number (percentage)**
Total AEs	158 (98%)	34 (94%)	11 (100%)	No patients 85 years or older were included in studies 14001, 15002 or 15003.
Serious AEs – Total	46 (29%)	20 (56%)	4 (36%)	
- Fatal	9 (6%)	3 (8%)	0	
- Hospitalization/prolong existing hospitalization	40 (25%)	19 (53%)	4 (36%)	
- Life-threatening	6 (4%)	4 (11%)	2 (18%)	
- Disability/incapacity	No data			
- Other (medically significant)	No data			
AE leading to drop-out	13 (8%)	8 (22%)	2 (18%)	
Psychiatric disorders	42 (26%)	9 (25%)	1 (9%)	
Nervous system disorders	94 (58%)	26 (72%)	8 (73%)	
Accidents and injuries	6 (4%)	0	0	
Cardiac disorders	22 (14%)	6 (17%)	2 (18%)	
Vascular disorders	33 (20%)	4 (11%)	5 (45%)	
Cerebrovascular disorders	4 (2%)	1 (3%)	1 (9%)	
Infections and infestations	74 (46%)	13 (36%)	3 (27%)	
Anticholinergic syndrome	0	0	0	
Quality of life decreased	0	0	0	
Sum of Orthostatic hypotension, Fall, Loss of consciousness, Syncope, Dizziness, Ataxia, Fracture	51 (32%)	20 (56%)	6 (55%)	
Other AEs appearing more frequently in older patients				
Fatigue	53 (33%)	16 (44%)	5 (45%)	
Anaemia	37 (23%)	14 (39%)	4 (36%)	

Immunological events

No data regarding immunological events was submitted as part of this application.

Safety related to drug-drug interactions and other interactions

Please refer to the PK section.

Discontinuation due to adverse events

Table 92: TEAEs Leading to Permanent Treatment Discontinuation (cut-off 30 July 2018)

Preferred Term	Efficacy-eval NTRK Fusion Cancers (N=93)	Overall NTRK Fusion Cancers Safety (N=137)	Overall Safety (N=208)
Patients with TEAE	5 (5%)	5 (4%)	23 (11%)
Disease progression	1 (1%)	1 (1%)	3 (1%)
Alanine aminotransferase increased	1 (1%)	1 (1%)	2 (1%)
Aspartate aminotransferase increased	1 (1%)	1 (1%)	2 (1%)
Dehydration	0 (0%)	0 (0%)	2 (1%)
Abdominal pain	0 (0%)	0 (0%)	1 (0%)
Acute myeloid leukaemia	0 (0%)	0 (0%)	1 (0%)
Amylase increased	0 (0%)	0 (0%)	1 (0%)
Asthenia	0 (0%)	0 (0%)	1 (0%)
Brain oedema	0 (0%)	0 (0%)	1 (0%)
Cellulitis	0 (0%)	0 (0%)	1 (0%)
Decreased appetite	0 (0%)	0 (0%)	1 (0%)
Dyspnoea	0 (0%)	0 (0%)	1 (0%)
Enterocutaneous fistula	0 (0%)	0 (0%)	1 (0%)
Fatigue	0 (0%)	0 (0%)	1 (0%)
Hyponatraemia	0 (0%)	0 (0%)	1 (0%)
Intestinal perforation	1 (1%)	1 (1%)	1 (0%)
Jaundice	1 (1%)	1 (1%)	1 (0%)
Lipase increased	0 (0%)	0 (0%)	1 (0%)
Metastases to central nervous system	0 (0%)	0 (0%)	1 (0%)
Muscular weakness	0 (0%)	0 (0%)	1 (0%)
Nausea	0 (0%)	0 (0%)	1 (0%)
Pericardial effusion	0 (0%)	0 (0%)	1 (0%)
Pleural effusion	0 (0%)	0 (0%)	1 (0%)
Small intestinal obstruction	1 (1%)	1 (1%)	1 (0%)
Syncope	0 (0%)	0 (0%)	1 (0%)
Vomiting	0 (0%)	0 (0%)	1 (0%)

Patients are counted once within each preferred term.
Reported adverse event terms were coded using MedDRA dictionary (version 18.1).
Adverse events are sorted in decreasing order of frequency based on the Overall Safety Analysis Set.
Percentages are calculated based on the number of patients in the column heading as the denominator.

TEAE leading to treatment discontinuation were reported in 11 % in the Overall Safety Analysis set.

Table 93: Reasons for treatment discontinuation for Adult Patients Treated at Recommended Dose

Status	Efficacy-eval NTRK Fusion Cancers (N=19)	Overall NTRK Fusion Cancers Safety (N=37)	Overall Safety (N=42)
Reason Treatment Discontinued[c]			
Protocol Deviation	2 (3%)	2 (2%)	2 (2%)
Disease Progression	24 (38%)	26 (30%)	56 (45%)
Adverse Event	2 (3%)	2 (2%)	6 (5%)
Subject Decision	2 (3%)	2 (2%)	5 (4%)

Table 94: Reason for treatment discontinuation for Paediatric Patients Treated at Recommended Dose

Status	Efficacy-eval NTRK Fusion Cancers (N=19)	Overall NTRK Fusion Cancers Safety (N=37)	Overall Safety (N=42)
Reason Treatment Discontinued[c]			
Disease Progression	3 (16%)	4 (11%)	7 (17%)
Adverse Event	0 (0%)	0 (0%)	1 (2%)
Other	2 (11%)	3 (8%)	3 (7%)
Death	0 (0%)	0 (0%)	1 (2%)

[a] Initial NDA visit Cutoff date 17-Jul-2017.
[b] Paediatrics (<18 years). For Cohorts 1 and 2, the target was based on dosing calculation tables in Appendix C of Protocol 15003. For Cohort 3, the target dose was capped at 100 mg BID.
[c] Status as of 30-Jul-2018.
[d] Disease progression includes patients with clinical progression.
Percentages are calculated based on the number of patients in the column heading as the denominator.
Source: Table 2004 (Visit Cutoff 30 JUL 2018)

Very few patients at recommended dose discontinued treatment due to adverse events in the Overall Safety set (adult and paediatric patients 5 % and 2 % respectively).

Post marketing experience

No post marketing experience was available at the time of review of this application.

2.6.1. Discussion on clinical safety

The initial submission with data cut-off date of 19 February 2018 included an integrated, pooled safety set named the "Overall Safety Analysis Set" (N=176) comprising data from all adult and paediatric patients who had a malignancy with or without a documented NTRK gene fusion and who received at least one dose of larotrectinib in studies LOXO-TRK-14001 (≥18 years of age, N = 70), LOXO-TRK-15002 (acronym NAVIGATE, ≥ 12 years of age, N = 63), and LOXO-TRK-15003 (acronym SCOUT, paediatric population, N = 43). In study LOXO-TRK-14001, 8 (11 %) patients had TRK fusion cancers whilst the majority were patients with non-TRK fusion cancers (62 [89 %]). In the paediatric study LOXO-TRK-15003, 9 (21 %) patients with non-TRK fusion cancers and 34 (79 %) patients with TRK fusion cancers were enrolled. In terms of the paediatric population, the number of patients enrolled according to the following age cohorts was: < 1 year → 9 (5 %), 1 - < 6 years → 14 (8 %), 6 - <12 years → 8 (5 %), 12 - < 18 years →13 (7 %).

None of the studies included a comparator which hampers the evaluation of the safety data. A deficiency in the presentation of the integrated safety set was that it did not distinguish data between adults and paediatric patients or malignancies with or without a documented NTRK gene fusion. Neither were there any safety data presented in the patient populations treated at recommended larotrectinib dose. Following the assessment of the safety update (new cut-off date of 30 July 2018) with an additional 5.5 months follow-up and an increase in number to a total of 56 paediatric and 152 adult patients comprising the overall safety analysis set, it may be agreed that overall no clinically relevant change to the toxicity profile of larorectinib has been identified when compared to the one characterised based on the data from the 19 February 2018 data cut-off date. In terms of patients treated at the recommended dose, no clinically relevant differences were observed as compared to those treated with a non-recommended dose. The safety profiles between the Overall safety set and the NTRK cancer fusion analysis sets are also similar. In terms of safety profiles between adults and the paediatric population, some differences in safety profiles are noted. Likewise, some differences in safety profiles are observed between the paediatric age-cohorts (see below).

At the new data cut-off date, 45% of the patients in the Overall Safety set (N=208) and 68 % of the patients in the Overall NTRK Fusion Cancers set (N=137) were still on study treatment. The most common reasons for discontinuation was disease progression (87 patients [42 %]). Overall the low number of patients that discontinued study drug due to AEs is recognised (≤ 4 %).

Median time on treatment was longer for the Efficacy-evaluable NTRK fusion cancers (N=93) and the Overall NTRK fusion cancers analysis sets (N=137) than that for the Overall Safety Analysis Set (N=208) with 12.1 months [range 0.66 to 40.7], 7.5 months [range 0.03 to 40.7] and 4.1 months [range 0.03 to 40.7] respectively. The shorter median time on treatment for the latter group is not unexpected as the Overall Safety set includes also patients without the NRTK gene fusions whom are not expected to respond to the study drug.

Overall the vast majority of patients needed dose modifications (≥ 80 %). Dose reductions were needed for 15 % of the patients in the Overall Safety Analysis Set however dose reductions due to AEs were infrequent with a low proportion of 9 %. Reasons for dose increases were mainly due to increase in BMI/ weight gain.

Almost all patients in the Overall Safety Analysis set experienced at least one TEAE (98 %) with the vast majority of TEAEs considered related to study drug (80 %). By System Organ Class (SOC) in the Overall safety set, TEAEs were most commonly reported in the SOCs of Gastrointestinal disorders (70 % [Nausea 28 %]), General disorders and administration site conditions (63 % [Fatigue 36 %]), Nervous system disorders (62 % [Dizziness 29 %]), Musculoskeletal and connective tissue disorders (51 % [Myalgia 16 %]), Respiratory, Thoracic and Mediastinal disorders (51 % [Cough 26 %]), Metabolism and Nutrition disorders (50 % Decreased [appetite 13 %]), Investigations (48 % [AST and ALT increase 26 % each]), Infection and infestation (43 %), and Blood and lymphatic system disorders (41 % [Anaemia 26 %]). Similar proportions were observed in the Overall NTRK Fusion Cancers set.

In terms of TEAEs by Preferred Term (PT), most commonly reported were Fatigue (36 %), Dizziness (29 %), Nausea (28 %), Constipation (27 %), ALT increase, Anaemia, AST increase and Cough (26 % each), Vomiting (24 %9, Diarrhoea (23 %) and Pyrexia (18 %). Similar proportions and patterns were observed in the Overall NTRK Fusion Cancers set.

In regard to TEAEs by severity, Grade 3 were reported in 82 patients (39 %) and grade 4 in 13 patients (6%) in the Overall safety set. The most common reported Grade 3 event was anaemia (10 %) and the remaining reports were isolated cases without any distinguishable pattern. The same is observed in terms of Grade 4 events. The corresponding proportions for the Efficacy-eval NTRK Fusion cancer set is similar. A total of 40 reports (43 %) of Grade 3 and 8 cases (9 %) of Grade 4 with the most common Grade 3 event being also anaemia (10 %). In the Overall NTRK Fusion Cancers Safety, Grade 3 events were reported in 36 % and Grade 4 in 7 %.

The most common adverse drug reactions (≥ 20%) of VITRAKVI in order of decreasing frequency were fatigue (32%), increased ALT (31%), dizziness (30%), increased AST (29%), constipation (29%), nausea (26%), anaemia (24%), and vomiting (20%).

A total of 34% of patients in the Overall Safety Analysis set experienced at least one SAE during treatment with similar results for the NTRK gene fusion analysis set (28%) and the Efficacy-evaluable NTRK gene fusion analysis set (33%). Most commonly reported in the Overall Safety Analysis set (aside from disease progression which is not regarded as an AE) was pyrexia (3 %), diarrhoea and sepsis (each reported in 2 %).

Neurologic reactions including dizziness, gait disturbance and paraesthesia were reported in patients receiving larotrectinib. For the majority of neurologic reactions, onset occurred within the first three months of treatment. Withholding, reducing, or discontinuing larotrectinib dosing should be considered, depending on the severity and persistence of these symptoms (see sections 4.4 and 4.8 of the SmPC).

The majority of ALT and AST increases occurred in the first 3 months of treatment. Liver function including ALT and AST assessments should be monitored before the first dose and monthly for the first 3 months of treatment, then periodically during treatment, with more frequent testing in patients who develop transaminase elevations. Withhold or permanently discontinue larotrectinib based on the severity. If withheld, modify the larotrectinib dose when resumed (see section 4.4 of the SmPC).

Ninety eight (98) % of the adult population treated with the recommended dose of larotrectinib in the Overall Safety Set (N=152), had any TEAEs with Fatigue (38 %), Dizziness (37 %), Nausea (30 %) and Anaemia (26 %) being the most commonly reported events. AST and ALT elevations were reported in 23 % and 22 % respectively. Adult patients treated with the recommended dose in the Overall NTRK Fusion Cancers Safety Set (N=90) shows a similar pattern with Dizziness (41 %) followed by Fatigue (38 %), Nausea (30 %) and Anaemia (24 %). AST and ALT elevations were reported in 26 % and 27 % respectively.

The safety profile in the paediatric population (< 18 years) was consistent in types of reported adverse reactions to those observed in the adult population.

Of the paediatric patients treated with the recommended dose in the Overall Safety Set (N=56), 98 % had any TEAEs with ALT and AST elevations most commonly reported (38 % and 36 % respectively, followed by Vomiting (36 %), Neutrophil decreased (31 %), Constipation (29 %) and Diarrhoea (29 %). For the paediatric patients treated with the recommended dose in the Overall NTRK Fusion Cancers Safety Set (N=47), similarity is also noted to that of the paediatric Overall safety Set with ALT and AST elevations most commonly reported (41 % and 35 % respectively, followed by Vomiting (35 %), Diarrhoea (32 %), Neutrophil decreased (30 %), and Constipation (30 %).

Regarding the paediatric subgroups (the limited number of patients in each age cohort is recognised), in the youngest age-group (Infants and Toddlers, N=18), 94 % had any TEAEs with ALT elevations, Vomiting and Diarrhoea (61 % each) most commonly reported followed by Pyrexia and Constipation (56 % each), Neutrophil count decreased (50 %), AST elevations, Cough and Anaemia (44 % each) and Fatigue (39 %). For the Children age group (N=23), the corresponding proportions are 96 % with any TEAE and most commonly reported are AST and ALT elevations (39 %) each, Vomiting (35 %), Cough, Diarrhoea and headache (30 % each). In terms of Adolescents (N=15), all patients reported any TEAE with Pain in extremity most commonly reported (40 %), followed by AST elevation, Neutrophil count decreased, Nausea and Headache most commonly reported (33 %) ALT elevation, Vomiting and Dizziness (27 % each). It is concluded that there are some differences in the safety profile between the paediatric age cohorts with more TEAEs reported in the youngest age cohort for e.g. neutropenia, anaemia, pyrexia, GI disorders (diarrhoea, vomiting, constipation and nausea) and weight increase as compared to the older age cohorts. In terms of the Overall NTRK Fusion Cancers Safety Set (N=47), with a total of 18 patients enrolled in the age group of Infants and Toddlers, 20 patients in the Children age group and 9 patients in the Adolescents group, the pattern and proportions of reported PTs are similar to that of the Paediatric Subgroup Overall Safety Set above.

In terms of fatal events and based on the initial data cut-off date of 19 February 2018, 30 deaths were reported at any time. A total of 11 patients (6%) experienced TEAEs with a fatal outcome within 30 days of receiving larotrectinib in the Overall Safety Analysis set (5 patients in study LOXO-TRK-14001, 4 in LOXO-TRK-15002 and 2 in LOXO-TRK-15003). All were attributed to either disease progression (7 patients) or to a complication of the primary malignancy. None of the cases were considered related to the investigational drug. The reasons for deaths that occurred > 30 days after the last dose of study drug were disease progression (14 patients) and unknown cause (4 patients).

Permanent discontinuation of larotrectinib for treatment emergent adverse reactions, regardless of attribution occurred in 3% of patients (one case each of ALT increase, AST increase, intestinal perforation, jaundice, small intestinal obstruction). The majority of adverse reactions leading to dose reduction occurred in the first three months of treatment.

Most common causes were disease progression and AT/ALT elevations (1 % each). Notably, 5 % permanently discontinued in the NTRK Fusion Cancers analysis sets. The reasons leading up to treatment discontinuations are more or less all isolated cases with no discernible pattern in terms of reasons for discontinuation. Many of them may also be considered as disease related. Moreover, very few patients treated at recommended dose discontinued treatment due to adverse events in the Overall Safety set (adult and paediatric patients 5 % and 2 % respectively). The majority of adverse reactions leading to dose reduction occurred in the first three months of treatment.

In the concentration-QTc modelling, a shortening of QTcF during treatment with larotrectinib was observed, however the clinical relevance of this finding cannot be established. This information is included in section 5.1 of the SmPC (see also Clinical Pharmacology discussion).

The comparison of safety profile between age group is very difficult due to the wide heterogeneity of the population in term of tumour histology and prior treatments. The nature of the reported AE seems to be consistent between age groups with difference in incidence.

The safety profile in elderly patients (≥ 65 years) seems to be consistent with that seen in younger patients (< 65 years). An increase in terms of reported serious AEs and hospitalisation with increasing age is observed. Nervous system disorders were more commonly reported in the elderly as compared to patients < 65 vs. 65-74. Also fatigue and anaemia were more frequently reported in the older cohort. The adverse reactions gait disturbance, and blood alkaline phosphatase increased were more frequent in patients of 65 years or older.

There are no data from the use of larotrectinib in pregnant women. The use of larotrectinib should be avoided during pregnancy. Women of reproductive potential should be advised to use highly effective contraception during treatment with larotrectinib and for at least one month after the final dose (see 2.3 Non-clinical aspects and section 4.6 of the SmPC).

It is unknown whether larotrectinib/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with larotrectinib and for 3 days following the final dose.

Larotrectinib may have a moderate influence on the ability to drive and use machines. Dizziness and fatigue have been reported in patients receiving larotrectinib, mostly Grade 1 and 2 during the first 3 months of treatment. This may influence the ability to drive and use machines during this time period. Patients should be advised not to drive and use machines, until they are reasonably certain larotrectinib therapy does not affect them adversely (see section 4.7 of the SmPC).

There is limited experience of overdose with larotrectinib. Symptoms of overdose are not established. In the event of overdose, physicians should follow general supportive measures and treat symptomatically.

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

There are concerns regarding the potential long-term toxicity and developmental effects of larotrectinib in paediatric patients. The MAH should submit the final report of study LOXO-TRK-15003 (SCOUT) with particular focus on neurodevelopment including cognitive function.

2.6.2. Conclusions on the clinical safety

From an overall safety perspective (adult patients and paediatric patients), larotrectinib appears reasonably tolerable and the toxicity is considered to be manageable with appropriate risk minimization measures as evidenced by the low treatment discontinuation rate. The long-term safety profile of larotrectinib will be further characterized in the post-marketing setting through registry and a non-intervention post authorisation safety study (see RMP).

The CHMP considers the following measures necessary to address the missing safety data in the context of a CMA:

- In order to further investigate the long-term toxicity and developmental effects of larotrectinib in paediatric patients, with particular focus on neurodevelopment including cognitive function, the MAH should submit the final report of study LOXO-TRK-15003 (SCOUT) including 5 year follow up data.

2.7. Risk Management Plan

Safety concerns

Table 94 Summary of safety concerns

Important identified risks	None
Important potential risks	Severe neurologic reactions Severe drug-induced liver injury Serious infections secondary to neutropenia Impairment of neurodevelopment in paediatric patients
Missing information	Use in pregnancy and lactation Long-term safety

Pharmacovigilance plan

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Study LOXO-TRK-15002, a Phase 2 multicentre, open-label study in patients 12 years of age and older with advanced cancer harbouring a fusion of *NTRK1*, *NTRK2*, or *NTRK3* Ongoing	To determine the ORR as determined by an independent radiology review committee and measured by the proportion of subjects with best overall confirmed response of CR or PR by the RECIST 1.1, or RANO criteria, as appropriate, following treatment with Vitrakvi® in subjects age 12 and older with an advanced cancer harbouring a fusion involving *NTRK1*, *NTRK2*, or *NTRK3* (collectively referred to as *NTRK* gene fusions) for each tumour-specific disease cohort.	Severe neurologic reactions Severe drug-induced liver injury Serious infections secondary to neutropenia Impairment of neurodevelopment in paediatric patients Use in pregnancy and lactation Long-term safety	FPFV LPLV CSR	OCT 2015 Q1 2021 Q2 2024
Study LOXO-TRK-15003, A Phase 1/2 study of the oral TRK inhibitor LOXO-101 in paediatric patients with advanced	Phase 1: To determine the safety of oral Vitrakvi® (larotrectinib; LOXO-101), including DLT, in paediatric patients with advanced solid	Severe neurologic reactions Severe drug-induced	FPFV	OCT 2015

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
solid or primary central nervous system tumours Ongoing	or primary CNS tumours. Phase 2: To determine the ORR, following treatment with Vitrakvi® in paediatric subjects with an advanced cancer harbouring a fusion involving *NTRK1*, *NTRK2*, or *NTRK3* (collective referred to as *NTRK* gene fusions). To create an updated PopPK model in paediatric patients between 1 month and 6 years of age. To collect long-term use safety and efficacy data in paediatric patients.	liver injury Serious infections secondary to neutropenia Impairment of neurodevelopment in paediatric patients Use in pregnancy and lactation Long-term safety	LPLV CSR	Q3 2020 Q1 2027
Category 3 - Required additional pharmacovigilance activities				
Study LOXO-TRK-14001, a Phase 1 multicentre, open-label, dose escalation and expansion study in adult patients with an advanced solid tumour Ongoing	To determine the safety of oral Vitrakvi® (also known as LOXO-101 or larotrectinib), including DLT, in adult patients with an advanced solid tumour; to characterise the PK properties, to describe antitumor activity, and to identify the MTD and/or the appropriate dose of Vitrakvi® for further clinical investigation.	Severe neurologic reactions Severe drug-induced liver injury Serious infections secondary to neutropenia Use in pregnancy and lactation Long-term safety	FPFV LPLV CSR	MAY 2014 Q2 2021 Q2 2022
Non-Interventional PASS (ON-TRK) Planned	To evaluate, under real-world conditions, the safety and effectiveness of Vitrakvi® in patients with locally advanced or metastatic TRK fusion cancer for whom a decision to treat with larotrectinib has been made before enrollment.	Severe neurologic reactions Severe drug-induced liver injury Serious infections secondary to neutropenia Impairment of neurodevelopment in paediatric patients Use in pregnancy and lactation Long-term safety	FPFV LPFV (all cohorts) LPLV (all cohorts excl. paediatric) LPLV (paediatric) Final CSR excl. paediatric Final CSR (Paediatric)	Q2 2019 Q2 2022 Q2 2024 Q2 2027 Q2 2025 Q2 2028
Patient Registry	EURACAN is the ERN for	Severe	Annual	annually

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
European Reference Network (ERN)- for adult rare solid cancers EURACAN Planned	adult rare solid cancers comprised of 66 sites across Europe. The network aims to reach all EU countries within 5 years and develop a referral system to ensure at least 75 % of patients are treated in a EURACAN centre. The EURACAN Genomic registry will be set up to collect genomic, clinical and safety data. The current French registry (SIRIC-OSIRIS: https://en.e-cancer.fr/OSIRIS-a-national-data-sharing-project) will be expanded through the EURACAN network. Bayer will receive annual summary results (efficacy and safety) in counterpart of its support to the EURACAN registry	neurologic reactions Severe drug-induced liver injury Serious infections secondary to neutropenia Use in pregnancy and lactation Long-term safety	summary results	

Risk minimisation measures

Table 95 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Severe neurologic reactions (Important potential risk)	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC Sections 4.8; 5.3) Routine risk communication recommending specific clinical measure to address the risk: • Caution patients about driving and operating machinery (SmPC 4.7) • Consider dose modification/s (SmPC 4.2; 4.4) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities**: Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, and in post-marketing experience. Further evaluation as an Adverse Event of Special Interest (AESI) in ongoing clinical trials: LOXO-TRK-14001, LOXO-TRK-15002, LOXO-TRK-15003
Severe drug-induced liver injury (Important potential	**Routine risk minimisation measures:** Routine risk communication so that an	**Additional pharmacovigilance activities**: Further evaluation in a

Table 95 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
risk)	informed decision can be made (SmPC sections: 4.2; 4.8; 5.2) Routine risk communication recommending specific clinical measure to address the risk: • Liver function monitoring (SmPC 4.2; 4.4) • Consider dose modification/s (SmPC 4.2; 4.4) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None	Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, and in post-marketing experience. Further evaluation as an AESI in ongoing clinical trials LOXO-TRK-14001, LOXO-TRK-15002, LOXO-TRK-15003
Serious infections secondary to neutropenia (Important potential risk)	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 4.8) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities**: Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, and in post-marketing experience. Further evaluation in ongoing clinical trials LOXO-TRK-14001, LOXO-TRK-15002, LOXO-TRK-15003

Table 95 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Impairment of neurodevelopment in paediatric patients (Important potential risk)	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 5.3) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities**: Further evaluation in a Non-Interventional PASS (ON-TRK), and in post-marketing experience. Further evaluation in ongoing clinical trials LOXO-TRK-15002, LOXO-TRK-15003
Use in pregnancy and lactation (Missing information)	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 5.3) Routine risk communication recommending specific clinical measure to address the risk: • Highly effective contraception in both males and females (SmPC 4.6) • Pregnancy test prior to treatment initiation (SmPC 4.6) • Discontinuation of breastfeeding in nursing mothers (SmPC 4.6) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities**: Further evaluation in a Non-Interventional PASS (ON-TRK) evaluation of annual summary results obtained from the (ERN)-EURACAN registry, and in post-marketing experience. Further evaluation in ongoing clinical trials LOXO-TRK-14001 LOXO-TRK-15002, LOXO-TRK-15003
Long-term safety (Missing information)	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 4.8) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities**: Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, and in post-marketing experience. Further evaluation in ongoing clinical trials LOXO-TRK-14001, LOXO-TRK-15002, LOXO-TRK-15003

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.6 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.

2.9. 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 26 November 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.10. New Active Substance

The applicant declared that larotrectinib has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers larotrectinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.11. Product information

2.11.1. 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.*

2.11.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, VITRAKVI (larotrectinib) 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 indication is independent of tumour type/histology - as follows:

"VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display 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 no satisfactory treatment options (see sections 4.4 and 5.1)."

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

Currently there are no EU approved specific targeted therapies for patients with *NTRK* fusion-positive cancer and there are no European national consensus guidelines or literature references with recommendations for the clinical management of such patients, who are clinically managed based on care standards for the tumour site of origin. However, following the approval of larotrectinib in the US, larotrectinib has been included in the American National Comprehensive Cancer Network (NCCN) clinical practice guidelines for common cancer types such as colon cancer, non-small cell lung cancer and melanoma.

In the EU, initial treatments generally include surgery and radiotherapy; and radioactive iodine for thyroid cancers. Systemic therapy options (including chemotherapy and treatment with biologics) are then considered. Some of the conditions encompassed by the indication are rare and generally associated with NTRK fusions, and without any satisfactory therapeutic options (e.g., salivary gland cancer of the MASC type). In other cases, the *NTRK* fusion-positive cancers constitute a small subgroup of a more common condition (e.g., colorectal cancer), for which several lines of treatment exist that have a documented clinical benefit in the overall disease population.

This application concerns a disease setting where there is no available therapy that is likely to have a positive B/R balance for the patient, or patients who only have a chance at cure at the cost of mutilating surgery. This is a population with a high unmet medical need.

3.1.3. Main clinical studies

The efficacy of larotrectinib is based on preliminary data from three currently ongoing trials:

- Study 14001 (LOXO-TRK-14001) is a dose-finding Phase 1/2 trial in adults with advanced solid tumours with or without NTRK gene fusions
- Study 15003 (LOXO-TRK-15003) is a dose-finding Phase 1/2 trial in paediatric patients with advanced solid tumours or primary CNS malignancies with or without NTRK gene fusions

- Study 15002 (LOXO-TRK-15002) is a Phase 2 basket trial in adolescent and adult patients with NTRK fusions

Interim data from these three studies were pooled together into a main efficacy analysis set denoted "the extended primary analysis set 2" (ePAS2). This is based on a third interim analysis with data cut-off date 30 July 2018, whereas the initial pooled analysis set (used for initial FDA New Drug Application) was named the PAS (data cut-off 17 July 2017).

The ePAS2 consists of patients from the 3 studies who met the criteria:

- Documented *NTRK* gene fusion (with exception for Infantile fibrosarcoma where *NTRK* fusion is a known feature of the disease; all patients had *NTRK* fusion, at least inferred, however)
- Non-CNS primary tumour
- At least 1 measurable lesion at baseline as assessed by RECIST v1.1
- Received at least 1 dose of larotrectinib

The primary endpoint for the pooled data analysis was objective response rate (ORR) by independent review committee (IRC). The pooled populations therefore also required sufficient follow-up for IRC, defined as at least 6 month's follow-up or discontinuation.

3.2. Favourable effects

Results in the ePAS2

The main efficacy analysis set is the pooled ePAS2, which consists of 93 patients. At the time of data cut-off 57% have treatment ongoing and 31% have experienced disease progression. The median time on treatment is 12.1 months, 14 patients (15%) have died, and 34 patients (37%) have had a PFS-event (death or disease progression).

The ORR by IRC was 72% (n=67/93, 95% CI: 62, 81%), and ORR by investigator assessment (INV) was 80%. The agreement rate between IRC and INV assessments was 90%.

The median change in target tumour lesions sizes was a decrease of 66%.

The time to response (TTR) median was 1.8 months by IRC and INV (IRC 25th, 75th percentiles: 1.71, 1.94 months). A vast majority of responding patients did so at the first tumour evaluation.

The duration of response (DoR) median was not reached by IRC or INV; of the 67 responding patients 47 (70%) were still in response at the time of analysis (IRC). 72% of responding patients had a tumour response that lasted 6 months or more, and 44% 12 months or more.

The progression-free survival (PFS) event-rate was 37% (IRC) and 38% (INV) in the ePAS2, and the median was 27.4 months (95% CI: 13.8, NE) by IRC and 28.3 months (95% CI: 15.2, NE) by investigator assessments. The PFS rate at 6 months was 77%, and the PFS rate at 12 months was 64% (95% CI: 51, 76%) by IRC.

The overall survival (OS) event-rate was 15% and the median was consequently not reached. The OS median follow-up time was 16.7 months (25th, 75th percentiles: 9.3, 23.0 months). The OS rate at 12 months was 88% (95% CI: 81, 95%).

Subgroup analyses

The ORR (IRC) was 68% (95% CI: 55, 79%) for patients with age ≥ 18 years (n=65); and 82% (95% CI: 63, 94%) for patients with age < 18 years (n= 28). Patients aged ≥ 65 years (n=15) had a response rate of 56% (95% CI: 31, 78%). It should be noted that age groups co-vary with tumour type.

The ORRs per NTRK fusion type was 63% (95% CI: 47, 78%) for *NTRK1* (n=41), 33% (95% CI: 1, 91%) for *NTRK2* (n=3), and 82% (95% CI: 68, 91%) for *NTRK3* (n=49). Note the wide confidence intervals.

The observed objective responses rates were highly variable across the studied tumour types, from 0% ORR in single patients with breast cancer, cholangiocarcinoma and pancreatic cancer to 100% in the 4 patients with GIST tumours.

Among 9 patients with primary CNS tumours who were excluded from the ePAS2 based on tumour type, but fulfilled the other criteria, 1 had an objective response (PR by INV).

3.3. Uncertainties and limitations about favourable effects

Clinical aspects

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.

Mechanisms for primary and secondary resistance mechanisms to larotrectinib have been addressed in the SmPC, and will be further investigated in the post-authorisation setting as part of the CMA conditions.

The application is considered lacking in prospectively studied cohorts that could provide an unbiased estimate of ORR. The uncertainty about the magnitude of the effect estimate due to these circumstances is of importance with respect to SmPC claims, and further strengthens the case for the non-comprehensiveness of available data. A prospective cohort is required to produce an unbiased estimate of efficacy.

The non-randomised design further hampers the assessment of particularly the time-dependent outcomes. The small efficacy data base raises issues with regard to the representativeness in relation to the indication sought, encompassing any solid tumour type. This aspect will be to some extent addressed during the post-marketing study and external controls. This uncertainty is stated in the SmPC (see section 4.4)

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 Annex II and RMP).

3.4. Unfavourable effects

By System Organ Class (SOC) in the Overall safety set (N=208), TEAEs were most commonly reported in the SOCs of Gastrointestinal disorders (70 % [Nausea 28 %]), General disorders and administration site conditions (63 % [Fatigue 36 %]), Nervous system disorders (62 % [Dizziness 29 %]), Musculoskeletal and connective tissue disorders (51 % [Myalgia 16 %]), Respiratory, Thoracic and Mediastinal disorders (51 % [Cough 26 %]), Metabolism and Nutrition disorders (50 % Decreased [appetite 13 %]), Investigations (48 % [AST and ALT increase 26 % each]), Infection and infestation (43 %), and Blood and lymphatic system disorders (41 % [Anaemia 26 %]). Similar proportions were observed in the Overall NTRK Fusion Cancers set.

By Preferred Term (PT), most commonly reported were Fatigue (36 %), Dizziness (29 %), Nausea (28 %), Constipation (27 %), ALT increase, Anaemia, AST increase and Cough (26 % each), Vomiting (24 %9, Diarrhoea (23 %) and Pyrexia (18 %). No relevant change was observed in the Overall NTRK Fusion Cancers set.

Grade 3 were reported in 82 patients (39 %) and grade 4 in 13 patients (6%) in the Overall safety set. The corresponding proportions for the Efficacy-eval NTRK Fusion cancer set and the Overall NTRK Fusion Cancers Safety set are similar.

A total of 34 % in the Overall Safety Analysis set experienced at least one SAE during treatment with similar results for the NTRK gene fusion analysis set (28 %) and the Efficacy-evaluable NTRK gene fusion analysis set (33 %). Most commonly reported in the Overall Safety Analysis set (aside from disease progression which is not regarded as an AE) was pyrexia (3 %), diarrhoea and sepsis (each reported in 2 %).

Neurologic reactions including dizziness, gait disturbance and paraesthesia were reported in patients receiving larotrectinib. For the majority of neurologic reactions, onset occurred within the first three months of treatment. Withholding, reducing, or discontinuing larotrectinib dosing should be considered, depending on the severity and persistence of these symptoms (see section 4.4 of the SmPC).

The majority of ALT and AST increases occurred in the first 3 months of treatment (see section 4.2 and 4.4 of the SmPC).

In terms of safety profiles between adults and the paediatric population, a difference is observed. Whilst the adult population treated with the recommended dose in the Overall Safety Set were most commonly reported for Fatigue (38 %), Dizziness (37 %), Nausea (30 %) and Anaemia (26 %), the paediatric patients treated with the recommended dose had ALT and AST elevations most commonly reported (38 % and 36 % respectively, followed by Vomiting (36 %), Neutrophil decreased (31 %), Constipation (29 %) and Diarrhoea (29 %).

There are also some differences in safety profiles between the paediatric age-groups (the limited number of patients in each age cohort is recognised). There are more TEAEs reported in the youngest age cohort for e.g. neutropenia, anaemia, pyrexia, GI disorders (diarrhoea, vomiting, constipation and nausea) and weight increase as compared to the older age cohorts. In the youngest age-group (Infants and Toddlers, N=18), 94 % had any TEAEs with ALT elevations, Vomiting and Diarrhoea (61 % each) most commonly reported followed by Pyrexia and Constipation (56 % each), Neutrophil count decreased (50 %), AST elevations, Cough and Anaemia (44 % each) and Fatigue (39 %). For the Children age group (N=23), the corresponding proportions are 96 % with any TEAE and most commonly reported are AST and ALT elevations (39 %) each, Vomiting (35 %), Cough, Diarrhoea and headache (30 % each). In terms of Adolescents (N=15), all patients reported any TEAE with Pain in extremity most commonly reported (40 %), followed by AST elevation, Neutrophil count decreased, Nausea and Headache most commonly reported (33 %) ALT elevation, Vomiting and Dizziness (27 % each).

Overall the vast majority of patients needed dose modifications (≥ 80 %). Dose reductions were needed for 15 % of the patients in the Overall Safety Analysis Set however dose reductions due to AEs were infrequent with a low proportion of 9 %.

TEAE leading to treatment discontinuation were reported in 11 % in the Overall Safety Analysis set which is deemed within in an acceptable range for an oncology study and raises no concern. Most common causes were disease progression and AT/ALT elevations (1 % each). Notably, 5 % permanently discontinued in the NTRK Fusion Cancers analysis sets.

None of the cases of 30 fatal events were considered related to the investigational drug. The reasons for deaths that occurred > 30 days after the last dose of study drug were disease progression (14 patients) and unknown cause (4 patients).

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety is currently limited which is addressed in the RMP and included as Missing information in the safety specifications. Several studies imposed as specific obligations or as additional pharmacovigilance activities will address it (see RMP).

There is potential for on-target central effects of larotrectinib in humans (neurologic reactions) due to the mechanism of action (neurotrophin signalling). Neurological events are kept under active monitoring in post-marketing setting. "Impairment of neurodevelopment in paediatric patients" and "Severe neurologic reactions" are included as important potential risks in the RMP.

The indication of larotrectinib in children covers all ages, with a body-size adjusted dose (100 mg/m2) for the smallest children up to a BSA of 1 m2, followed by the adult dose from 1 m2. The Applicant has aimed at a dose producing similar exposure in children as in adults receiving 100 mg BID. The simulated plots from the population pharmacokinetic model however show that children aged <3 months (based on 4 subjects) are predicted to have a >3-fold higher larotrectinib exposure, and the older age groups 5-50% higher larotrectinib exposure than adults. There is uncertainty in the predicted exposure in the smallest children, due to few subjects included in each age group, and thus not enough data available to be able to propose an alternative (lower) dose in children.

Although the proposed paediatric dose may have a positive benefit/risk given the convincing efficacy results and manageable short-term side effects observed, it appears to give a larotrectinib exposure higher than adult exposure, in particular in the smallest children. To avoid unnecessary overexposure, and potential risks for long-term side effects, the Applicant has committed to collect more PK data in children, and potentially update the dose recommendations to match the paediatric exposure to the exposure that has been shown to be safe and effective in adults.

3.6. Effects Table

Table 96: Effects Table for Vitrakvi in the treatment of NTRK gene fusion-positive advanced solid tumours (Data cut-off: Efficacy: 30 July 2018; Safety: 19 February 2018)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence / Comment
Favourable Effects					
Extended primary analysis set 2 (ePAS2)	**Pooled study population, NTRK fusion-positive**	**N**	**93**	**N/A**	**Evaluable patients from studies 14001, 15002 and 15003 pooled** Issues of multiplicity and bias due to the adaptive design cause the efficacy outcomes likely to be inflated
Objective response rate [a] (ORR) by IRC	Proportion with CR or PR	% (n)	72 (67)	N/A	Post-hoc pooling and exclusion of CNS cohort.
Time to response (TTR) by IRC in responding pts	Median 25th, 75th percentiles Min-Max	months	1.81 1.71, 1.94 0.95-14.55		TTR was consistent at 1.8 months by IRC and INV, respectively.
Duration of response (DoR) by IRC	Median 95% CI Min-Max	months	NE 17.3, NE 1.6+, 38.7+	N/A	70% (47/67 responding patients) still in response. Immature data.

Unfavourable Effects					
	Unit	Overall safety Analysis set N=176	Adult pop with NTRK fusion cancers at rec dose N=70	Paediatric pop with NTRK fusion ca at rec dose N=35	Uncertainties/ Strength of evidence
Grade 3 - Anaemia - Neutrophil decrease - Hypophosphataemia	%	39 10 4			
Grade 4 -	%	6			

Abbreviations: CNS= Central nervous system, N= total number, n= number, N/A= not applicable, NE = not evaluable
[a] : RECIST 1.1. Confirmation of response was required in this analysis.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the context of advanced cancer that has exhausted established therapeutic options, or does not have any, an outstanding ORR along with clinically meaningful DoR is considered sufficient to establish clinical benefit. Further, given that NTRK fusions are common only in rare cancers, and rare in all common cancers, the applicant's approach with a drug development program lacking dedicated studies in any particular histology is acceptable as a basis for the proposed indication.

Although there is uncertainty about the precise magnitude of effect, both due to the study conduct (see above), and since the understanding of the extent that tissue of origin is an effect modifier is incomplete, the observed overall ORR of 72% is considered outstanding. Also when the ORR results divided into adult (68%) and paediatric (82%) patients, results in both subgroups are considered compelling.

A short time to response (TTR) is considered of value in the treatment of any metastatic tumour since tumour shrinkage may reduce tumour symptoms. In patients with critical visceral disease or patients at risk of debilitating events (e.g. paralysis due to spine involvement) a short TTR is even more important. The consistently short median time to response of 1.8 months observed for larotrectinib is therefore considered of high clinical value. The median change in tumour size was 66% (i.e. including patients with PD as best response), greater than what is commonly seen for anticancer drugs, and is of clinical value for the same reason, i.e. reduction of tumour can reduce symptoms.

Due to the immaturity of the efficacy data, the median duration of response was not reached. Based on the present median time on treatment of 12.1 months, a median response duration of around 12 months may be expected in the ePAS2 analysis set. This would generally be considered a clinically relevant duration of response, regardless of line of treatment in metastatic solid tumours.

From an overall safety perspective (including data from the safety update) larotrectinib appears reasonably tolerable and the toxicity is considered to be manageable with appropriate risk minimization measures as evidenced by the low treatment discontinuation rate.

One main concern is the potential for on-target central effects of larotrectinib in humans (neurologic reactions) due to the mechanism of action (neurotrophin signalling). Neurological events are kept under active monitoring in post-marketing setting and "Impairment of neurodevelopment in paediatric patients" and "Severe neurologic reactions" are specifically included as important potential risks in the RMP. Further, the applicant has committed to further populating the popPK model to potentially allow for future refinement (i.e. lowering) of the dose in the smallest individuals.

3.7.2. Balance of benefits and risks

Overall the level of pharmacodynamic activity seen is impressive. Activity may be lower in certain tumour types, albeit still highly clinically relevant in the treatment setting defined by the indication. Furthermore, concomitant genetic alterations may theoretically impact the level of activity. Notwithstanding this, the explorative and adaptive nature of the study program, the immaturity of DoR data, the single arm nature of the studies, as well as the limitations of the data with respect to understanding the extent that tissue origin might act as an effect modifier, available data are considered non-comprehensive. Therefore, a Conditional Marketing Authorisation rather than a full MA is relevant.

Furthermore, the paediatric indication is acceptable in the setting of a CMA, given that the applicant commits to provide further data on paediatric exposure post approval.

The overall toxicity of larotrectinib appears manageable with appropriate risk minimisation measures as recommended in the SmPC. The safety profile is thus not considered to negatively impact the B/R balance of larotrectinib.

3.7.3. Additional considerations on the benefit-risk balance

This is the first contemporary example of a sought indication that is tumour type independent; therefore, the regulatory evaluation will set a precedent with regards to the evaluation of such applications.

As comprehensive data on the product are not available, a conditional marketing authorisation was proposed by the CHMP during the assessment, after having consulted the applicant.

Conditional marketing authorisation and the key specific obligation

Due to the small sample size of the presented data, comprehensive data on the product are not available; uncertainties remain on the precise estimates of efficacy based on a larger sample size in terms of objective response rate and response duration, and long term endpoints (OS, PFS); therefore, a conditional marketing authorisation is considered appropriate.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating, life-threatening disease where there is an unmet medical need.

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.

The main areas of non-comprehensive data are:

Efficacy:

- The benefit in subgroups of patients based on histology. This may be studied in terms of ORR and DoR in prospective single-arm studies encompassing a broad variety of tumour types.

- The requirement for unbiased estimate of ORR and DoR. This may be studied in a prospective cohort study.

- The size of treatment benefit on time-dependent outcome measures (OS, PFS);

- Resistance mechanisms and the role of concomitant oncogenic drivers to further characterise efficacy in different subgroups.

Safety: The size of the safety data base is limited, particularly given that this is a first-in-class pharmacological agent. Furthermore, the long-term safety follow-up is limited. Neurodevelopment in paediatric patients is a concern based on preclinical data. Finally, more pharmacokinetic data should be generated in small children, where drug exposure at the recommended doses may be higher than in the adults, to allow a reappraisal of the appropriate dose.

In order to fulfil a comprehensive data package, the Applicant as part of study LOXO-TRK-15002 (NAVIGATE) will submit a prospective cohort of 75 patients, for which at least 1 year of follow-up is available, and will perform an overall pooled analysis where the target population includes the ePAS2/SAS3 cohort (with the updated data) along with the prospective cohort, which would give increased precision of the estimates for the ORR and DoR.

This interventional single arm cohort has several overlapping aims. First, there is a need for a traditional corroboration of ORR in the target population in the light of a pivotal dataset emerging from several exploratory studies based on data-driven decisions, which may have led to an inflated ORR estimate. Furthermore, there is a need to provide a more precise estimate of efficacy in common cancers where NTRK fusions are rare, based on lower available efficacy estimates in such patients compared to those seen in rare cancers where NTRK-fusions are common or pathognomonic.

On this basis, specific sub-cohorts of patients with lung cancer, colorectal cancer, melanoma and non-secretory breast cancer have been agreed. Concomitant with such goals, there are also aspects related to uncertainties in the overall assumption that the presence of NTRK-fusions in a given histology is a predictor that larotrectinib will have activity. The underlying concern here is that the relationship between biomarker and response may be abolished by tissue-specific bypass mechanisms. From this perspective, the goal of the study would be to identify any "outlying" histologies that may exist.

For this purpose, the applicant has committed to enrol 200 additional patients(75 already enrolled) in NAVIGATE (LOXO-TRK-15002) and as part of the SCOUT study (LOXO-TRK-15003) within a 36 month period post approval. Eighty patients will be recruited in the common tumour types and 120 in the other tumour types. The applicant will discuss with the Agency whether enrolment should continue. The applicant will submit a pooled analysis together with the results of the prospective data in isolation.

The applicant will enrol at least 9 and up to 20 patients in total in each of the identified common tumour type subgroups (lung, melanoma, colorectal cancer, non-secretory breast), and pre-specifies rules for conclusions of adequate/inadequate clinical activity.

Furthermore, the applicant is proposing that the relevance of clinical efficacy in a given histology would be subject to review in case of no responses in 9 patients. If that occurs in the prospective cohort, the applicant should alert the Agency. In order to decide whether "inadequate response" has been identified in certain tumour types, the applicant will follow a Bayesian approach as a methodological rule and conventional approach. The applicant will inform the Agency if the criteria of "inadequate response" according to the Bayesian approach is fulfilled for any particular histology.

The data submitted as part of this specific obligation will refine the understanding of the B/R in certain subpopulations.

The SCOUT study (15003) will be amended to allow investigation of the long-term toxicity and developmental effects of larotrectinib in paediatric patients, with particular focus on neurodevelopment including cognitive function, using established instruments. In addition, monitoring and investigator support in the ongoing non-investigational study (NIS) will be increased to ensure high quality data on efficacy and safety.

Finally in order to further confirm the appropriate dose recommended in paediatric patients, the MAH has committed to submit an updated pop PK model based on additional PK sampling in patients aged 1 month to 6 years from study LOXO-TRK-15003 (SCOUT).

- Unmet medical needs will be addressed, as given the qualification of the indication to patients that have no remaining satisfactory treatment options, it is ascertained that a major therapeutic advantage over available therapies has been shown.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. The intended indication will provide patients with no satisfactory treatment options available, an alternative which has shown outstanding ORR along with clinically meaningful DoR sufficient to demonstrate clinical benefit.

3.8. Conclusions

The overall B/R of Vitrakvi in the indication:

"VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display 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 no satisfactory treatment options (see sections 4.4 and 5.1). "

is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that larotrectinib is not similar to Onivyde, Rubraca, Nexavar, Yondelis, Cometriq, Bavencio, Lutathera, Zejula, Qarziba, Lartruvo and Mepact within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of VITRAKVI is favourable in the following indication:

VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display 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 no satisfactory treatment options (see sections 4.4 and 5.1).

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 medical prescription.

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 shall submit the first periodic safety update report 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.

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 larotrectinib and to investigate the primary and secondary resistance mechanisms, the MAH should submit a pooled analysis for the increased sample size including the final report of study LOXO-TRK-15002 (NAVIGATE).	30 June 2024
In order to further investigate the long-term toxicity and developmental effects of larotrectinib in paediatric patients, with particular focus on neurodevelopment including cognitive function, the MAH should submit the final report of study LOXO-TRK-15003 (SCOUT) including 5 year follow up data.	31 March 2027
In order to further confirm the appropriate dose recommended in paediatric patients, the MAH should submit an updated pop PK model based on additional PK sampling in patients aged 1 month to 6 years from study LOXO-TRK-15003 (SCOUT).	30 September 2021

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that larotrectinib is a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0182/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.