Amsterdam, 27 March 2025
EMA/52156/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

VITRAKVI

Larotrectinib

Procedure no: EMEA/H/C/004919/P46/009

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	02 Dec 2024	02 Dec 2024	☐
☐	CHMP Rapporteur Assessment Report	06 Jan 2025	19 Dec 2024	☐
☐	CHMP members comments	20 Jan 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	23 Jan 2025	22 Jan 2025	☐
☐	RSI:	30 Jan 2025	30 Jan 2025	☐
☐	Submission by	25 Feb 2025		☐
☐	Re-start	26 Feb 2025	26 Feb 2025	☐
☐	CHMP Rapporteur Assessment Report	12 Mar 2025	17 Mar 2025	☐
☐	CHMP members comments	17 Mar 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20 Mar 2025	n/a	☐
☒	CHMP adoption of conclusions:	27 Mar 2025	27 Mar 2025	☐

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1. Introduction

On 13 November 2024, the MAH submitted a completed paediatric study for Larotrectinib (Vitrakvi), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The following Annex II.E specific obligations are listed in the current SmPC:

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).	31 March 2025
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

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the PIP03 for the larotrectinib paediatric clinical study 20290 was prepared in accordance with the approved Paediatric Investigational Plan (EMEA-001971-PIP03-18-M02, decision date 11 Aug 2022) and completes the paediatric development of larotrectinib.

2.2. Information on the pharmaceutical formulation used in the study

Larotrectinib was administrated as capsules or oral solution.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Larotrectinib PIP03 report PH-003410 for the larotrectinib paediatric clinical study 20290 (ex LOXO-TRK-15003; EudraCT number: 2016-003498-16; EU-CT number: 2022-502668-20-00.

The PIP03 report evaluated the treatment of paediatric patients from birth to less than 18 years of age with primary central nervous system (CNS) tumours harbouring a neurotrophic tyrosine receptor kinase (NTRK) gene fusion.

The evaluation included efficacy, safety, pharmacokinetics (PK), and biomarker results based on a subset of patients with primary CNS tumour from study 20290 (SCOUT). Furthermore, efficacy, safety, and palatability results for a subset of patients who exclusively received the new oral solution in study 20290 were presented.

Sensitivity analyses for efficacy and safety were presented by age groups for the pooled group of paediatric and adult primary CNS patients across studies 20289 and 20290 as well as supportive analyses of efficacy and safety for the pooled group of paediatric primary CNS patients across studies 20289 and 20290.

A historical data comparison of study 20290 with data from the Children's Brain Tumour Network (CBTN) database and from the CNSonTRK database was also presented for exploratory efficacy endpoints.

2.3.2. Study 20290 (SCOUT)

2.3.2.1. Description

Study 20290 is an ongoing, global, multicentre, open-label, phase 1/2 study in paediatric patients aged from birth to 21 years with advanced solid or primary CNS tumours. The study comprises a phase 1 dose escalation and dose expansion part and a phase 2 part. The phase 2 part consists of three paediatric cohorts with patients with NTRK gene fusion tumours.

The study enrolment ended on 18 May 2023 and results are summarised as of DCO 20 Jul 2023 (interim analysis).

2.3.2.2. Methods

2.3.2.2.1. Study participants

As of DCO, 154 patients were included in study 20290 and constituted the full analysis set (FAS). Of these, 24 were included in the phase 1 dose escalation part, 17 in the phase 1 dose expansion part, and 113 in the phase 2 part.

2.3.2.2.2. Treatments

The phase 1 larotrectinib doses varied from 9.6 mg/m^2 to 100 mg/m^2 BID (maximum 100 mg BID) depending on which of the three phase 1 cohorts the patients were enrolled in.

The phase 2 larotrectinib dose was 100 mg/m^2 BID, with a maximum of 100 mg BID.

Patients who had surgery and achieved negative margins or had a confirmed response, i.e., either partial response (PR) for one year for locally advanced disease or stable disease (SD) for a period of two years for low-grade glioma, may have their larotrectinib treatment held and enter a wait and see period (drug holiday) as assessed by the investigator and agreed with the sponsor.

2.3.2.2.3. Objectives and endpoints

Phase 1

The primary objective of the phase 1 part is to characterize safety and dose limiting toxicity (DLT), and secondary objectives are to characterize the PK, identify the maximum tolerated dose (MTD), antitumour activity of larotrectinib, and quality of life.

Phase 2

The primary objective of the phase 2 part is to describe antitumor activity with overall response rate (ORR) as primary endpoint. Secondary endpoints are duration of response (DOR), clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS), as well as safety, concordance

between NTRK profiling, and postoperative staging. Quality of life (QoL) and bone health are exploratory endpoints.

2.3.2.2.4. Statistical methods

The interim analysis data of study 20290 described below are based on investigator assessments.

2.3.2.3. Results

2.3.2.3.1. Baseline data

The median age of patients was 5.13 years (range 0.1 to 20.5), including two patients (1.3%) aged <1 month and 14 patients (9.1%) aged ≥16 years. In total, 71 (46.1%) patients were female and 83 (53.9%) were male.

NTRK gene fusion was identified in 146/154 (94.8%) of the tumours.

The most common malignancies were infantile fibrosarcoma (31.8%), primary CNS tumours (29.9%), and soft tissue sarcoma (27.3%).

2.3.2.3.2. Pharmacokinetics

Pharmacokinetic results were not updated for the current interim report of study 20290.

2.3.2.3.3. Efficacy results

Table 1 Summary of efficacy results as assessed by the Investigator (FAS), Interim analysis results study 20290

Efficacy parameter	*NTRK* Fusion N=146	Non-*NTRK* Fusion N=8	Total N=154
Treatment period (including Wait and See): 1			
Overall Response Rate, n (%) [a]			
Number of evaluable participants	134	5	139
Number of participants with overall response (CR + PR + pCR)	95	0	95
ORR, %	71	0	68
[95% CI] for ORR [c]	[62, 78]	NC	[60, 76]
Clinical Benefit Rate, n (%) [b, c]			
Number of evaluable participants	145	5	150
Number of participants with CBR [c]	134 (92)	0	134 (89)
[95% CI] for CBR	[87, 96]	NC	[83, 94]
Duration of response, months [d, f]			
Number of participants with confirmed CR or PR	95	0	95
Median DOR	58.6	NE	58.6
[95% CI] for median	[23.9, NE]	[NE, NE]	[23.9, NE]
Range	0.9+, 82.9+	NE, NE	0.9+, 82.9+
Duration of Follow-up for DOR (months) [e]			
N	95	0	95
Median	36.9	NE	36.9
25th, 75th percentile	11.9, 55.6	NE, NE	11.9, 55.6
Duration of PFS, months [d, f]			
Median	48.8	1.1	37.4
[95% CI] for median	[27.5, NE]	[0.4, 1.7]	[22.1, NE]
Range	0.03+, 83.7+	0.4, 1.9	0.03+, 83.7+
Duration of Follow-up for PFS (months) [e]			
Median	39.2	NE	39.2
25th, 75th percentile	10.8, 57.6	NE, NE	10.8, 57.6
Duration of OS (months), Kaplan-Meier estimate [d, f]			
Median	NE	3.7	NE
[95% CI]	[NE, NE]	[0.4, 7.2]	[NE, NE]
Range	2.1+, 87.4+	0.4, 12.5	0.4, 87.4+
Follow-up time for OS (months), Kaplan-Meier estimate [e]			
Median	50.2	NE	50.2
25th percentile, 75th percentile	30.4, 62.9	NE, NE	29.9, 62.9

BOR = best overall response, CBR = confirmed benefit rate; CI = confidence interval; CR = complete response; DOR = duration of response; FAS = full analysis set; N = total number of participants (100%); n = number of participants in category/with event; NC = not calculated; NE = not estimable; *NTRK* = neurotrophic tyrosine receptor kinase; ORR = overall response rate; OS = overall survival; pCR = pathological CR; PFS = progression-free survival; PR = partial response; SD = stable disease.

[a] Excluded participants without measurable disease at baseline and participants continuing treatment without any postbaseline assessment,

[b] CBR (%) was defined as the proportion of participants with BOR of confirmed CR (including pCR), PR, or unconfirmed PR/CR and SD lasting ≥16 weeks following the initiation of larotrectinib. SD was measured from the date of the first dose of larotrectinib.

[c] 95% CI was calculated using Clopper-Pearson method.

[d] Based on Kaplan-Meier method. Minimum and maximum included the censored observations where using + after value indicates censoring.

[e] Based on inverse Kaplan-Meier method.

[f] 95% CI was calculated using Greenwood's formula.

No efficacy data per age group were submitted.

2.3.2.3.4. Safety results

Of the 154 patients who received larotrectinib, 76 (49.3%) were still on study treatment or in the wait and see period (n=43 and n=33, respectively). The remaining 78 (50.6%) patients had discontinued larotrectinib, mainly due to disease progression (n=41 [27%]).

The median larotrectinib dose received was 97.13 mg/m^2 BID (range 17.5, 120.1) and the median number of cycles of 28 days was 17.5 (range 1 to 95). The median study treatment duration was 15.40 (range 0.4 to 87.4) months.

Adverse events

In total 152/154 (98.7%) experienced a treatment-emergent adverse event (TEAE), of which 102 (66.2%) of the patients had TEAEs grade ≥3 and 69 (44.8%) had serious adverse events (SAEs). Study treatment discontinuation due to TEAEs was reported for 13 (8.4%) patients.

TEAEs by Preferred Term (PT) regardless of dose occurring in ≥25% of patients overall were:

- vomiting (51.3%)
- pyrexia (49.3%)
- ALT and AST increased (42.2% and 41.6%, respectively)
- cough (38.3%)
- diarrhoea (35.7%)
- upper respiratory tract infection (33.8%)
- neutrophil count decreased (29.2%)
- anaemia (27.3%)
- constipation (26.0%)
- headache (25.3%)

The most commonly reported grade ≥3 TEAE was neutrophil count decreased (18.2%).

Several of the most commonly occurring TEAEs regardless of causality were reported with a higher incidence in infants and toddlers (birth to <24 months age group) compared with patients in all of the other age groups (children 2 to <12 years, adolescents 12 to <18 years, and young adults 18 to <21 years): vomiting, pyrexia, diarrhoea, upper respiratory tract infection, neutrophil count decreased, anaemia, and constipation.

Study treatment modifications and deaths

Overall, 148/154 (96.1%) of the patients had at least one dose modification (regardless of cause), of which 82 (53.2%) had a dose increase and 53 (34.4%) had a dose decrease.

Six (4.0%) patients died within 28 days of the last study dose. One patient died due to TEAE cerebellar haemorrhage, one due to TEAE sudden death, and four patients died due to disease progression (reported as TEAEs of medulloblastoma, glioblastoma multiforme, malignant neoplasm progression, and respiratory failure).

A total of 29 (18.8%) patients died >28 days after the last study dose, the majority due to disease progression.

2.3.3. Study PIP03

2.3.3.1. Description

To meet the reporting requirements of EMEA-001971-PIP03-18-M02, the patients presented in the main analyses in the PIP03 report are paediatric patients with a primary CNS tumour harbouring an NTRK gene fusion, i.e., a subset of the patients in study 20290 described above. This subset of patients is hereafter referred to as the `PIP03 population´.

The PIP03 population consists of patients from both phase 1 and phase 2 parts of study 20290.

DCO for the PI03 analyses was 18 May 2024.

2.3.3.2. Methods

2.3.3.2.1. Study participants

The PIP03 population comprised a total of 40 paediatric patients with primary CNS tumours harbouring NTRK gene fusions. Of these patients, 22 had high-grade gliomas (HGG), 13 had low-grade gliomas (LGG), and five had non-gliomas.

2.3.3.2.2. Treatments

All patients in the PIP03 population received larotrectinib 100 mg/m^2 BID, with maximum dose 100 mg BID.

2.3.3.2.3. Objectives

The primary objective of PIP03 was to support the approval of larotrectinib in paediatric patients <18 years of age with primary CNS tumours harbouring NTRK gene fusions.

The secondary objectives were to characterise NTRK1, NTRK2, and NTRK3 gene fusions by next-generation sequencing (NGS) from tumour biopsies and circulation tumour DNA (ctDNA), to evaluate potential biomarkers of response and resistance to larotrectinib, and PK analyses.

2.3.3.2.4. Endpoints

Primary endpoints

Phase 1: safety and tolerability

Phase 2: ORR by RANO criteria assessed by an independent radiology review committee (IRC)

Secondary endpoint

Phase 1 and 2: BOR according to RANO criteria, disease control rate (DCR), DOR, PFS, and OS as assessed by IRC.

Phase 2: palatability, safety and tolerability

Exploratory endpoints

Phase 1 and 2: QoL through Peds-QoL, assessment of functional performance status, assessment of pain by the Wong-Baker Faces scales in children ≥3 years of age, and neurocognitive assessment using the Ages & Stages Questionnaires, 3rd ed. (ASQ3).

2.3.3.2.5. Sample size justification

As agreed in the EMEA-001971-PIP03-18-M02 the following thresholds for ruling out efficacy were defined:

For HGG, an ORR of at least 35% with a power of 82.7% with 1-sided alpha = 0.056 to test ORR </=10% vs ORR >10%. An ORR of ≤10% will be ruled out if there are at least four responders among 15 patients.

For LGG, sustained (6 months) DCR to test DCR ≤30% vs. > 30% with 1-sided alpha = 0.05 and power of 69.0%. A sustained DCR of ≤30% will be ruled out if there are at least 6 out of 8 patients with disease control at 6 months.

2.3.3.2.6. Randomisation and blinding (masking)

Study 20290, comprising the PIP03 study, was open-label.

2.3.3.2.7. Statistical Methods

The current version of the statistical analysis plan for PIP03 is version 2.0 as off 28 June 2024.

The performed analyses in PIP03 are exploratory. According to the MAH, some comparisons may not be regarded as meaningful due to the small sample sizes.

The point estimate of the primary endpoint ORR will be calculated based on the maximum likelihood estimator (i.e., crude proportion of patients with best overall response of pCR, confirmed CR or confirmed PR). Patients with a non-confirmed CR or non-confirmed PR will be included in the ORR calculation but will not be considered as responders. Patients with no post-baseline tumour assessment (i.e. have a BOR of undefined) will be excluded from the calculation of ORR. The point estimate will be accompanied by a 2-sided 95% exact binomial confidence interval (CI) using the Clopper-Pearson method.

Secondary endpoint DCR is defined as the percentage of patients with either a pCR, confirmed CR, confirmed PR or SD. SD need to have a minimum duration of 16 weeks after first dose of larotrectinib.

Secondary endpoint DOR will be calculated for patients with CR, PR or pCR after resection surgery as their best overall response and is defined as the number of months from the start date of PR, pCR or CR (whichever response is recorded first) using the following formula:

DOR (months) = (Progression/Censoring Date – Response Start Date + 1) / 30.4375

At the time of study entry, HGG, LGG, and non-gliomas were assigned subtype and grade using the 2007 WHO Classification of Tumours of the CNS.

The latest paediatric investigational plan agreed with EMA/PDCO (EMEA-001971-PIP03-18-M02) specifies the analysis to be done by tumour type. For this PIP03, the tumour subtypes HGG, LGG, and non-glioma are used to further subdivide the CNS-only population.

2.3.3.2.8. Analysis sets

Analyses were performed using the following analysis sets:

<u>Safety analysis set</u>

The safety analysis set (SAF) used for safety evaluation included patients who fulfilled the following criteria:

- Received one or more doses of larotrectinib
- Had documented NTRK gene fusion as determined by local testing
- Had diagnosis of primary CNS cancer
- Were treated at the approved dose of 100 mg/m^2 BID with maximum dose of 100 mg
- Were <18 years of age.

<u>Efficacy analysis set</u>

The efficacy analysis set (EAS) was the main analysis set used for efficacy evaluation and consisted of patients in the SAF who had measurable disease at baseline as assessed by investigator and RANO or RECIST criteria 1.1.

Efficacy analysis set 2

The EAS2 consisted of patients in the SAF who had measurable disease at baseline as assessed by IRC and RANO criteria.

Palatability analysis set

Palatability, safety, and efficacy of the new oral solution was assessed in patients who were enrolled in study 20290 phase 2, exclusively took the new oral solution, and were recruited up to 12 months before the DCO of 18 May 2024 (i.e., all patients had ≥12 months of follow-up).

Patients without documented NTRK fusion and/or without primary CNS cancer and/or no measurable disease at baseline were also included in the palatability analysis set.

Safety analysis set 3

The safety analysis set 3 (SAS3) consisted of at pooled paediatric and adult population with primary CNS tumours included in studies 20290 and 20289. All patients had NTRK gene fusion positive tumours, had received at least one dose of larotrectinib and had received their first larotrectinib dose at least six months prior to the integrated analysis DCO (20 Jul 2023).

2.3.3.3. Results

2.3.3.3.1. Baseline data

Table 2 Patient demographics (PIP03 SAF)

	HGG (N=22)	LGG (N=13)	Non-glioma (N=5)	Total PIP03 SAF N=40
Age (years)				
Median	4.08	7.08	13.83	6.00
Range	0.2, 11.8	1.8, 14.7	5.0, 16.7	0.2, 16.7
Age category, n (%)				
1 month to <1 year	1 (5)	0	0	1 (3)
1 to <2 years	2 (9)	1 (8)	0	3 (8)
2 to <6 years	11 (50)	2 (15)	1 (20)	14 (35)
6 to <12 years	8 (36)	9 (69)	1 (20)	18 (45)
12 to <16 years	0	1 (8)	2 (40)	3 (8)
≥16 years	0	0	1 (20)	1 (3)
Sex, n (%)				
Female	14 (64)	8 (62)	1 (20)	23 (58)
Male	8 (36)	5 (38)	4 (80)	17 (43)
Race, n (%)				
White	14 (64)	10 (77)	3 (60)	27 (68)
Asian	5 (23)	1 (8)	1 (20)	7 (18)
Other	2 (9)	2 (15)	0	4 (10)
Black or African American	0	0	1 (20)	1 (3)
Declined to state	1 (5)	0	0	1 (3)
Ethnicity, n (%)				
Non-Hispanic or Latino	21 (95)	12 (92)	5 (100)	38 (95)
Hispanic or Latino	0	1 (8)	0	1 (3)
Declined to state	1 (5)	0	0	1 (3)
Body weight (kg)				
Median	18.05	25.80	45.10	21.20
Range	5.4, 44.0	16.0, 58.8	26.7, 72.3	5.4, 72.3
BSA (m^2)				
Median	0.73	0.91	1.39	0.82
Range	0.3, 1.3	0.6, 1.6	0.9, 1.9	0.3, 1.9

BSA = body surface area; HGG = high-grade glioma; LGG = low-grade glioma; N = total number of patients (100%); n = number of patients within category; PIP03 = pediatric investigational plan 03; SAF = safety analysis set

Note: due to rounding, percentages may sometimes not add up to 100% (e.g., for age categories).
Percentages are based on the number of patients (N) specified in the column header.
Baseline values are those measured closest to but not after the first dose of larotrectinib.

Table 3 Disease characteristics (PIP03 SAF)

	HGG [a] N=22	LGG [a] N=13	Non-glioma [a] N=5	Total PIP03 SAF N=40
Primary diagnosis, n (%)				
Primary CNS	22 (100)	13 (100)	5 (100)	40 (100)
Disease status at enrollment, n (%)				
Locally advanced	18 (82)	11 (85)	3 (60)	32 (80)
Metastatic	4 (18)	2 (15)	2 (40)	8 (20)
Time since initial diagnosis (years)				
Median	1.27	2.53	1.95	1.82
Range	0.1, 7.1	0.3, 9.6	0.9, 5.5	0.1, 9.6
Grade of disease at initial diagnosis, n (%)				
High	21 (95)	0	2 (40)	23 (58)
Low	0	12 (92)	1 (20)	13 (33)
Unknown	1 (5)	1 (8)	2 (40)	4 (10)
Stage at initial diagnosis, n (%)				
I	1 (5)	6 (46)	0	7 (18)
II	1 (5)	0	0	1 (3)
III	3 (14)	0	1 (20)	4 (10)
IV	5 (23)	0	0	5 (13)
Missing	12 (55)	7 (54)	4 (80)	23 (58)
Baseline performance status [b]				
Median	90.00	90.00	100.00	90.00
Range, n (%)	50.0, 100.0	50.0, 100.0	70.0, 100.0	50.0, 100.0
100	6 (27)	4 (31)	4 (80)	14 (35)
90	9 (41)	7 (54)	0	16 (40)
80	3 (14)	1 (8)	0	4 (10)
70	2 (9)	0	1 (20)	3 (8)
60	1 (5)	0	0	1 (3)
50	1 (5)	1 (8)	0	2 (5)

CNS = central nervous system; HGG = high-grade glioma; LGG = low-grade glioma; N = total number of patients (100%); n = number of patients within category; PIP03 = pediatric investigational plan 03; SAF = safety analysis set; WHO = World Health Organization
Percentages are based on the number of patients (N) specified in the column header.
Due to rounding, percentages may sometimes not add up to 100%.
Baseline values are those measured closest to but not after the first dose of larotrectinib.
[a] HGG, LGG, non-glioma at study entry based on the 2007 WHO grade classification.
[b] Based on Lansky or Karnofsky performance status scale as appropriate.

Table 4 NTRK gene fusion type (PIP03 SAF)

	HGG (N=22) n (%)	LGG (N=13) n (%)	Non-glioma (N=5) n (%)	Total PIP03 SAF N=40 n (%)
***NTRK* fusion**	**22 (100)**	**13 (100)**	**5 (100)**	**40 (100)**
***NTRK* gene fusion, n (%)**				
NTRK1	6 (27)	1 (8)	0	7 (18)
NTRK2	14 (64)	10 (77)	4 (80)	28 (70)
NTRK3	2 (9)	2 (15)	1 (20)	5 (13)
***NTRK* gene fusion partner, n (%)**				
GKAP1-NTRK2	1 (5)	1 (8)	1 (20)	3 (8)
NACC2-NTRK2	2 (9)	1 (8)	0	3 (8)
AGAP1-NTRK2	0	1 (8)	1 (20)	2 (5)
ETV6-NTRK3	1 (5)	1 (8)	0	2 (5)
KANK1-NTRK2	2 (9)	0	0	2 (5)
SPECC1L-NTRK2	2 (9)	0	0	2 (5)
TPM3-NTRK1	2 (9)	0	0	2 (5)
Other fusion [a]	12 (55)	9 (69)	3 (60)	24 (60)

HGG = high-grade glioma; LGG = low-grade glioma; N = total number of patients (100%); n = number of patients within category; *NTRK* = neurotrophic tyrosine receptor kinase; PIP03 = pediatric investigational plan 03; SAF = safety analysis set
Percentages are based on the number of patients (N) specified in the column header.
[a] In the PIP03 SAF: One patient each with *ATG16L1-NTRK2, BCAN-NTRK1, BCR-NTRK2, BCR-NTRK3, CDK5RAP2-NTRK2, CGN-NTRK1, EML1-NTRK2, GTF2I-NTRK2, KANK-NTRK2, KANK1-NTRK3, KANK2-NTRK2, KCTD16-NTRK2, KIF21B-NTRK1, MAP7D1-NTRK3, PHYHIPL-NTRK2, PRCC-NTRK1, PTPN13-NTRK2, QKI-NTRK2, SLMAP-NTRK2, STRN3-NTRK2, STRN4-NTRK2, TNS3-NTRK2, TP53-NTRK1, ZBTB10-NTRK2*

2.3.3.3.2. Prior and concomitant therapy

Most patients in the SAF (95%) received previous cancer treatment, most commonly prior systemic therapy (80%), prior surgery (63%), or prior radiotherapy (33%). Patients had received a median of 1.0 prior systemic therapies (range 1-8), and the best response to the last systemic treatment was most commonly SD (38%). Larotrectinib was the initial systemic therapy for 20% of patients.

All patients (100%) received concomitant medications. More than 30% of patients in the SAF received common supportive medications used in cancer patients, including paracetamol (70% of patients), ibuprofen (50%), and ondansetron (38%).

2.3.3.3.3. Efficacy results PIP03

Primary and secondary endpoints

Table 5 Efficacy results (PIP03 EAS and EAS2)

	EAS				EAS2			
	HGG (N=20)	LGG (N=9)	Non-glioma (N=5)	Total (N=34)	HGG (N=16)	LGG (N=8)	Non-glioma (N=3)	Total (N=27)
Best overall response, n (%) [a]								
CR	2 (10)	1 (11)	1 (20)	4 (12)	2 (13)	1 (13)	1 (33)	4 (15)
CR (confirmed)	2 (10)	1 (11)	1 (20)	4 (12)	2 (13)	1 (13)	1 (33)	4 (15)
PR	7 (35)	3 (33)	1 (20)	11 (32)	7 (44)	5 (63)	1 (33)	13 (48)
PR (confirmed)	7 (35)	3 (33)	1 (20)	11 (32)	7 (44)	5 (63)	1 (33)	13 (48)
SD [g]	8 (40)	4 (44)	1 (20)	13 (38)	5 (31)	1 (13)	0 (0)	6 (22)
PD	2 (10)	1 (11)	2 (40)	5 (15)	2 (13)	1 (13)	1 (33)	4 (15)
Not Evaluable	1 (5)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
ORR [b]								
Number of evaluable patients	16	6	3	25	16	8	3	27
CR (confirmed)	2 (13)	1 (17)	1 (33)	4 (16)	2 (13)	1 (13)	1 (33)	4 (15)
PR (confirmed)	7 (44)	3 (50)	1 (33)	11 (44)	7 (44)	5 (63)	1 (33)	13 (48)
ORR (CR + PR + pCR), n (%)	9 (56)	4 (67)	2 (67)	15 (60)	9 (56)	6 (75)	2 (67)	17 (63)
[95% CI] [c]	30, 80	22, 96	9, 99	39, 79	30, 80	35, 97	9, 99	42, 81
DCR [d]								
Number of evaluable patients	20	9	5	34	16	8	3	27
DCR, n (%)	16 (80)	8 (89)	3 (60)	27 (79)	13 (81)	7 (88)	2 (67)	22 (81)
[95% CI] [c]	(56, 94)	(52, 100)	(15, 95)	(62, 91)	(54, 96)	(47, 100)	(9, 99)	(62, 94)
Sustained DCR [e]								
Number of evaluable patients	20	9	5	34	16	8	3	27
DCR, n (%)	15 (75)	8 (89)	3 (60)	26 (76)	12 (75)	7 (88)	2 (67)	21 (78)
[95% CI] [c]	(51, 91)	(52, 100)	(15, 95)	(59, 89)	(48, 93)	(47, 100)	(9, 99)	(58, 91)
Any tumor regression [f]								
Number of evaluable patients	16	6	3	25	16	8	3	27
Any tumor regression	16 (100)	6 (100)	3 (100)	25 (100)	16 (100)	8 (100)	3 (100)	27 (100)
[95% CI] [c]	79, 100	54, 100	29, 100	86, 100	79, 100	63, 100	29, 100	87, 100
Best % change in tumor burden assessed by RANO [f]								
Number of evaluable patients, n	16	6	3	25	16	8	3	27
Mean	-67.9	-55.3	-81.1	-66.5	-67.9	-62.3	-81.1	-67.7
Median	-75.5	-85.4	-79.8	-79.8	-75.5	-83.3	-79.8	-80.1
Range	-100.0, 8.9	-100.0, 55.8	-100.0, -63.6	-100.0, 55.8	-100.0, 8.9	-100.0, 55.8	-100.0, -63.6	-100.0, 55.8

BOR = best overall response; CI = confidence interval; CR = complete response; DCR = disease control rate; EAS(2) = Efficacy analysis set (2); HGG = high-grade glioma; IRC = independent review committee; LGG = low-grade glioma; N = total number of patients (100%); n = number of patients within category; ORR = overall response rate; pCR = pathological complete response, previously referred to as surgical complete response; PD = progressive disease; PIP03 = pediatric investigational plan 03; PR = partial response; RANO = Response Assessment in Neuro-Oncology; SD = stable disease

Unless specified otherwise, percentages were based on the number of patients (N) specified in the column header.

[a] BOR was defined as the best response designation for each patient that was recorded between the date of the first dose of larotrectinib and the date of documented disease progression per RANO or the date of subsequent therapy or cancer-related surgery, whichever occurred first. The data presented within this table incorporate the correction of the data entry error in the adjudication of BOR for 1 patient (see Section 4.1.1.4 for further details).

[b] ORR was defined as the percentage of patients with a BOR of confirmed CR, pCR, or confirmed PR by RANO. CR or PR must have been confirmed by a repeat assessment no less than 28 days after the criteria for response were first met. For pCR, the post-surgical pathology evaluation served as confirmation. Excludes patients without measurable disease at baseline by Investigator (EAS) or IRC (EAS2) and patients continuing treatment without any post-baseline assessment.

[c] 95% CI was calculated using the Clopper-Pearson method.

[d] DCR (%) (also referred to as Clinical Benefit Rate in the protocol) was defined as the percentage of patients with BOR of confirmed CR (including pCR), confirmed PR, or SD which occurred 16 or more weeks after the first dose of larotrectinib.

[e] Sustained DCR (%) was defined as the percentage of patients with a BOR of confirmed CR (including pCR), confirmed PR, or SD, where SD was sustained for at least 6 months.

[f] Based on the sum of product of diameters for patients with measurable disease at baseline and assessed by RANO. Excludes patients without measurable disease at baseline and patients continuing treatment without any postbaseline assessment.

[g] Patient 20290-402-158 underwent surgical resection with no viable tumor cells and negative margins on postsurgical pathology evaluation and was assessed pCR by Investigator, but could not be considered pCR as radiological tumor assessment by IRC was SD.

Table 6 ORR (IRC-assessed) by NTRK gene fusion isoform in >2 patients in PIP03 – confirmed responses (PIP03 EAS and EAS2)

NTRK gene fusion isoform	EAS (N=34)				EAS2 (N=27)			
	N	N (evaluable) [a]	CR+PR+pCR	ORR [95% CI] [b]	N	N (evaluable) [a]	CR+PR+pCR	ORR [95% CI] [b]
Overall	34	25	15	60 [39, 79]	27	27	17	63 [42, 81]
GKAP1-NTRK2	3	2	0	NC [NC]	2	2	0	NC [NC]
NACC2-NTRK2	3	3	1	33 [1, 91]	3	3	1	33 [1,91]
AGAP1-NTRK2	2	0	NA	NC [NC]	-	-	-	-
ETV6-NTRK3 [c]	2	1	1	NC [NC]	1 [d]	1	1	NC [NC]
KANK1-NTRK2	2	2	2	NC [NC]	2	2	2	NC [NC]
Other	22	17	11	65 [38, 86]	20 [d]	20	14	70 [46, 88]

CI = confidence interval; CR = complete response; EAS(2) = Efficacy analysis set (2); IRC = independent review committee; N = total number of patients (100%); NA = not applicable; NC = not calculated; *NTRK* = neurotrophic tyrosine receptor kinase; ORR = overall response rate; pCR = pathological complete response, previously referred to as surgical complete response; PIP03 = pediatric investigational plan 03; PR = partial response

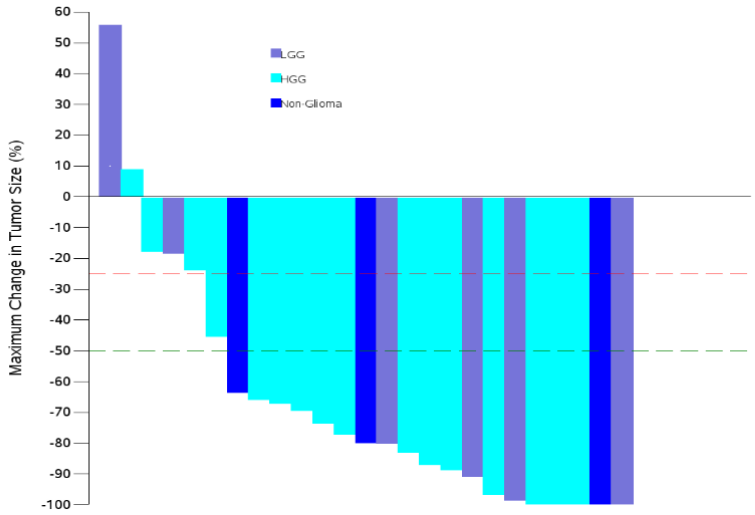
[a] Excluded patients without measurable disease at baseline and patients continuing treatment without any post-baseline assessment.

[b] 95% CI was calculated using the Clopper-Pearson method.

[c] Inferred *ETV6-NTRK3* combined with *ETV6-NTRK3*.

[d] In the EAS2, the patient with *ETV6-NTRK3* was included within the 20 patients with "Other" *NTRK* gene fusion isoforms since it did not meet the cut-off of at least 2 patients.

Figure 1 Waterfall plot of best change (IRC-assessed) in tumour size by CNS subtype (PIP03 EAS)



EAS = Efficacy analysis set; IRC = independent review committee; PIP03 = pediatric investigational plan 03; RANO = Response Assessment in Neuro-Oncology; RAPNO = Response Assessment in Pediatric Neuro-Oncology

Green dotted line = At least 50% reduction indicates a PR in the target lesions per RANO criteria.

Red dotted line = 25 to <50% reduction indicates a minor response in the target lesions per RAPNO criteria (Erker et al. 2020, Fangusaro et al. 2020)

Includes patients who have baseline measurable disease by the Investigator using RANO criteria.

Exploratory endpoints

Table 7 Time to response – IRC assessment (subgroup of EAS with confirmed CR or PR)

	HGG (N=9)	LGG (N=4)	Non-glioma (N=2)	Total (N=15)
Patients with best response of confirmed CR, pCR, or PR [a], n	9	4	2	15
Time to response (days) [b,c]				
Median	113.0	56.0	85.0	112.0
[95% CI]	56.0, 281.0	28.0, NE	58.0, NE	56.0, 113.0
Range	56.0, 1518.0	28.0, 56.0	58.0, 112.0	28.0, 1518.0
Time to response				
≤2 months	4 (44%)	4 (100%)	1 (50%)	9 (60%)
>2 to 4 months	1 (11%)	0	1 (50%)	2 (13%)
>4 to 6 months	1 (11%)	0	0	1 (7%)
>6 to 9 months	1 (11%)	0	0	1 (7%)
>9 months	2 (22%)	0	0	2 (13%)

CI = confidence interval; CR = complete response; EAS = Efficacy analysis set; HGG = high grade glioma; IRC = independent review committee; LGG = low grade glioma; N = total number of patients (100%); n = number of patients within category; NE = not estimable; pCR = pathological complete response; PR = partial response; RANO = Response Assessment in Neuro-Oncology Criteria; UICC = Union for International Cancer Control

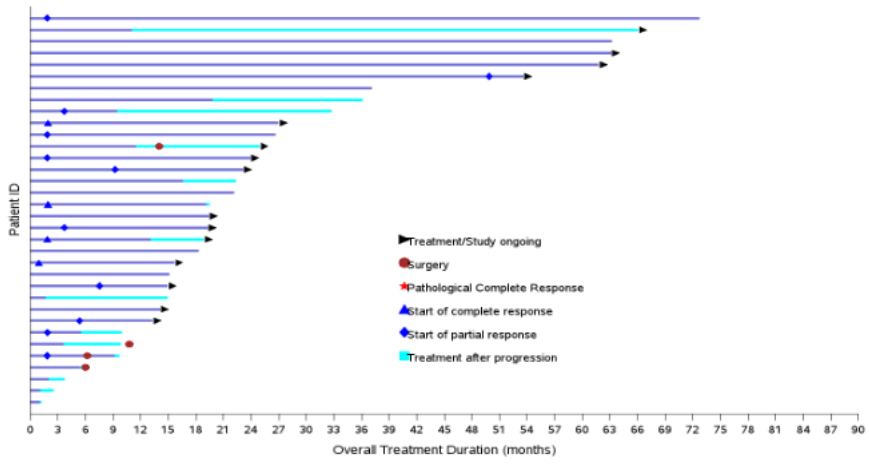
Percentages are based on the number of patients (N) in the column header as the denominator.

[a] Status as of cutoff visit. Based on IRC assessments. The data presented within this table incorporate the correction of the data entry error in the adjudication of BOR for 1 patient (see Section 4.1.1.4 for further details).

[b] Time to response was defined as the time (days) from start of study treatment to the date of first observed response (first measured CR or PR). Patients who underwent surgical resection with pathology reports showing negative margins, no viable tumor cells, and a UICC classification of R0, in addition to an IRC radiological RANO response of CR or NE, will be considered a CR on the date of surgical resection (pCR).

[c] Median duration of response was estimated based on Kaplan-Meier method. 95% CI was calculated using the Greenwood's formula.

Figure 2 Swimmer plot of time to response an overall treatment duration (IRC-assessed) (PIP03 EAS)



EAS = Efficacy analysis set; N = total number of patients (100%); IRC = independent review committee; PIP03 = pediatric investigational plan 03

Disease assessments based on IRC assessment. Only time on treatment is displayed.

Includes patients who have a response by IRC available (N=34).

Table 8 Duration of response (IRC-assessed) (PIP03 EAS and EAS2) – amended by the Rapporteur

	PIP03 EAS				PIP03 EAS2			
	HGG (N=20)	LGG (N=9)	Non-glioma (N=5)	Total (N=34)	HGG (N=16)	LGG (N=8)	Non-glioma (N=3)	Total (N=27)
Patients with response status [d]	9 (45)	4 (44)	2 (40)	15 (44)	9 (56)	6 (75)	2 (67)	17 (63)
Response status, n (%)								
Progressed	3 (15)	0	1 (20)	4 (12)	3 (19)	1 (13)	1 (33)	5 (19)
Censored	6 (30)	4 (44)	1 (20)	11 (32)	6 (38)	5 (63)	1 (33)	12 (44)
Alive without disease progression	5 (25)	4 (44)	1 (20)	10 (29)	5 (31)	5 (63)	1 (33)	11 (41)
Surgical resection of tumor without complete pCR	1 (5)	0	0	1 (3)	1 (6)	0	0	1 (4)
DOR (months) [a, b]								
Median [95% CI]	11.3 [3.7, NE]	NE [NE, NE]	17.2 [NE, NE]	NE [11.3, NE]	11.3 [3.7, NE]	NE [12.2, NE]	17.2 [NE, NE]	NE [11.3, NE]
Range	2.8+, 23.2+	12.9+, 70.9+	12.8, 17.2	2.8+, 70.9+	2.8+, 23.2+	9.2+, 70.9+	12.8+, 17.2	2.8+, 70.9+

The median follow-up for DOR in both the EAS and EAS2 was 12.9 months.

Table 9 Summary of progression-free survival (IRC-assessed) (PIP03 EAS and EAS2)

	PIP03 EAS				PIP03 EAS2			
	HGG (N=20)	LGG (N=9)	Non-glioma (N=5)	Total (N=34)	HGG (N=16)	LGG (N=8)	Non-glioma (N=3)	Total (N=27)
Patients with progression status, n [d] (%)	20 (100)	9 (100)	5 (100)	34 (100)	16 (100)	8 (100)	3 (100)	27 (100)
Progression status, n (%)								
Progressed or died	11 (55)	3 (33)	4 (80)	18 (53)	10 (63)	2 (25)	2 (67)	14 (52)
Censored	9 (45)	6 (67)	1 (20)	16 (47)	6 (38)	6 (75)	1 (33)	13 (48)
Alive without documented PD	8 (40)	6 (67)	1 (20)	15 (44)	5 (31)	6 (75)	1 (33)	12 (44)
Surgical resection of tumor without pCR	1 (5)	0	0	1 (3)	1 (6)	0	0	1 (4)
Duration of PFS (months) [a, b]								
Median [95% CI]	19.8 [5.6, NE]	50.8 [1.1, NE]	18.4 [1.7, NE]	19.8 [13.1, NE]	11.5 [5.4, NE]	NE [1.1, NE]	19.1 [1.7, NE]	19.1 [9.5, NE]
Range	1.1, 60.3+	1.1, 72.7+	1.7, 19.1	1.1, 72.7+	1.1, 52.6+	1.1, 72.7+	1.7, 19.1	1.1, 72.7+
Rate (%) [95% CI] of PFS [a, b]								
≥6 months	75 [55, 94]	89 [68, 100]	80 [45, 100]	79 [66, 93]	68 [45, 91]	88 [65, 100]	67 [13, 100]	74 [57, 91]
≥12 months	57 [34, 80]	89 [68, 100]	80 [45, 100]	70 [54, 85]	46 [20, 72]	88 [65, 100]	67 [13, 100]	61 [42, 80]
≥24 months	35 [10, 59]	89 [68, 100]	NE [NE]	43 [24, 63]	29 [4, 54]	66 [25, 100]	NE [NE]	38 [17, 60]
≥36 months	35 [10, 59]	89 [68, 100]	NE [NE]	43 [24, 63]	29 [4, 54]	66 [25, 100]	NE [NE]	38 [17, 60]
≥48 months	35 [10, 59]	59 [10, 100]	NE [NE]	36 [15, 57]	29 [4, 54]	66 [25, 100]	NE [NE]	38 [17, 60]
≥60 months	35 [10, 59]	30 [0, 78]	NE [NE]	29 [8, 50]	NE [NE]	66 [25, 100]	NE [NE]	38 [17, 60]
≥72 months	NE [NE]	30 [0, 78]	NE [NE]	29 [8, 50]	NE [NE]	66 [25, 100]	NE [NE]	38 [17, 60]
≥84 months	NE [NE]	NE [NE]	NE [NE]	NE [NE]	NE [NE]	NE [NE]	NE [NE]	NE [NE]
Duration of follow-up (months) [c]								
Median	25.1	25.6	NE	25.1	22.1	22.0	NE	22.0
25th percentile, 75th percentile	13.9, 59.1	15.2, 72.7	NE, NE	16.5, 59.1	13.9, 25.1	13.4, 29.1	16.5, NE	13.8, 29.1

+ denotes censored observations; CI = confidence interval; EAS(2) = Efficacy analysis set (2); HGG = high-grade glioma; IRC = independent review committee; LGG = low-grade glioma; N = total number of patients (100%); n = number of patients within category; NE = not estimable; pCR = pathological complete response, previously referred to as surgical complete response; PD = progressive disease; PFS = progression-free survival; PIP03 = pediatric investigational plan 03

Percentages are based on the number of patients (N) specified in the column header.

[a] Based on the Kaplan-Meier method.

[b] 95% CI was calculated using the Greenwood's formula.

[c] Based on an inverse Kaplan-Meier method.

[d] The data presented within this table incorporate the correction of the data entry error in the adjudication of BOR for 1 patient (see Section 4.1.1.4 for further details).

Table 10 Summary of overall survival (IRC-assessed) (PIP03 EAS and EAS2)

	PIP03 EAS				PIP03 EAS2			
	HGG (N=20)	LGG (N=9)	Non-glioma (N=5)	Total (N=34)	HGG (N=16)	LGG (N=8)	Non-glioma (N=3)	Total (N=27)
Patients who died, n (%)	8 (40)	1 (11)	1 (20)	10 (29)	7 (44)	1 (13)	1 (33)	9 (33)
Patients censored (alive), n (%)	12 (60)	8 (89)	4 (80)	24 (71)	9 (56)	7 (88)	2 (67)	18 (67)
Reason censored:								
Alive	11 (55)	8 (89)	4 (80)	23 (68)	8 (50)	7 (88)	2 (67)	17 (63)
Study discontinuation	1 (5)	0	0	1 (3)	1 (6)	0	0	1 (4)
Duration of OS (months) [a,b]								
Median [95% CI] [b]	32.7 [21.0, NE]	NE [3.2, NE]	NE [33.6, NE]	NE [32.7, NE]	32.7 [12.0, NE]	NE [3.2, NE]	NE [33.6, NE]	NE [22.9, NE]
Range [a]	4.9, 65.2+	3.2, 72.7+	18.3+, 75.7+	3.2, 75.7+	4.9, 65.2+	3.2, 72.7+	18.3+, 36.3+	3.2, 72.7+
Rate (%) [95% CI] of being alive [a, b]								
≥6 months	95 [85, 100]	89 [68, 100]	100 [100, 100]	94 [86, 100]	94 [82, 100]	88 [65, 100]	100 [100, 100]	93 [83, 100]
≥12 months	80 [62, 98]	89 [68, 100]	100 [100, 100]	85 [73, 97]	75 [54, 96]	88 [65, 100]	100 [100, 100]	81 [67, 96]
≥24 months	59 [35, 83]	89 [68, 100]	100 [100, 100]	73 [57, 90]	57 [30, 84]	88 [65, 100]]	100 [100, 100]	71 [53, 90]
≥36 months	49 [23, 76]	89 [68, 100]	75 [33, 100]	63 [43, 82]	43 [11, 74]	88 [65, 100]	50 [0, 100]	55 [31, 79]
≥48 months	49 [23, 76]	89 [68, 100]	75 [33, 100]	63 [43, 82]	43 [11, 74]	88 [65, 100]	NE [NE, NE]	55 [31, 79]
≥60 months	49 [23, 76]	89 [68, 100]	75 [33, 100]	63 [43, 82]	43 [11, 74]]	88 [65, 100]	NE [NE, NE]	55 [31, 79]
≥72 months	NE [NE, NE]	89 [68, 100]	75 [33, 100]	63 [43, 82]	NE [NE, NE]	88 [65, 100]	NE [NE, NE]	55 [31, 79]
Follow-up time for OS (months) [c]								
Median	36.1	39.7	52.5	36.3	25.7	26.8	36.3	26.8
25th percentile, 75th percentile	20.5, 61.5	20.8, 62.6	36.3, 75.7	22.7, 62.4	20.5, 53.0	22.7, 54.2	18.3, 36.3	22.7, 53.0

Sensitivity analyses

The results of the sensitivity analyses in which the CNS tumour subtypes were classified by the WHO 2021 classification were similar to those of the main analyses.

2.3.3.3.4. Efficacy results in study PIP03 palatability analysis set

A total of 17 patients from study 20290 phase 2 only received the new 2% oral larotrectinib solution and were enrolled in the palatability analysis set (please refer to `Treatments´ above). Of these, 10/17 (59%) were evaluable for palatability of the new oral solution.

At the time of DCO (18 May 2024), 10/17 (58.8%) patients were still on treatment or currently off treatment, whereas 7/17 (41.2%) had discontinued treatment. Three patients discontinued due to progression, three due to reason `other ´, and one had died. The median duration of treatment for the 17 patients was 18.2 months (range 2.5 to 51.4 months).

The ORR in the palatability analysis set was 82% (95% CI 57, 96), with seven patients (41%) having a BOR of CR and equally many a BOR of PR. One patient (6%) had a BOR of SD. The DCR was 885 (95% CI 64, 99). The median DOR was not estimable (NE) (95% CI 5.8, NE).

2.3.3.3.5. Efficacy results pooled paediatric and adult population

Supportive data were generated using pooled data on paediatric and adult patients with primary CNS tumours in the SAS3.

The SAS3 comprised 55 patients, of which 38 (69.1%) were <18 years of age and 17 (30.9%) were >18 years of age.

The IRC-assessed ORR in the SAS3 was 27% (95% CI 16, 41) with a BOR CR reported in three patients and PR in 12 patients. Median DOR was 12.2 months (95% CI 5.7, NE), with a median follow-up time of 11.9 months.

Overall, the paediatric patients in the SAS3 showed greater responses to larotrectinib than the adult patients. ORR in the paediatric subset was 37% (95% CI 22, 54), with three patients having a BOR of CR and 11 patients having a BOR of PR. Median DOR was 17.2 months (95% CI 5.7, NE).

2.3.3.3.6. Efficacy results in study 20290 compared to historical data

As requested by the PDCO, a retrospective, exploratory, externally-controlled matched comparison analysis to assess the therapeutic benefit/effectiveness of larotrectinib over the current standard of care (i.e., systemic therapy/regimen, e.g., single chemotherapy or combination chemotherapy, excluding radio-chemotherapy) was performed in paediatric patients with an NTRK fusion-positive primary CNS tumours.

The primary objective of the analysis was to compare the time to medical treatment failure (TTTF) between larotrectinib and systemic standard of care therapy. Patients from the study 20290 subset with primary CNS tumours (n=17) were matched with patients in an external control group (n=17) comprising eligible 'real-world' patients from the CBTN and CNSonTRK treated with at least one systemic anti-cancer regimen.

No formal statistical hypotheses were tested, and all comparisons were exploratory.

The median TTTF in the larotrectinib group was 23.0 months (95% CI 12.0. -) vs. 18.8 months (95% CI 6.7, -) in the external control group.

In the larotrectinib group, seven (41.2%) had treatment ongoing and 10 (58.8%) had discontinued treatment. In the external control group, all patients had discontinued treatment.

There was a limited amount of data available for the control group, which, together with the small sample size and small number of events, made subgroup comparisons difficult. Thus, these data must be interpreted with caution.

2.3.3.3.7. Safety results PIP03

The safety evaluation in PIP03 is based on the SAF primary CNS population, including patients from phases 1 and 2 of study 20290. Of these patients, seven were also included in the palatability analysis set. The most common reason for treatment discontinuation was disease progression (12 [30%] patients). One patient discontinued treatment due to death.

Treatment exposure and duration

At DCO, 16 (40%) of the SAF patients were still on study treatment, four (10%) were off treatment in the wait and see period, and 20 (50%) had discontinued study treatment.

Table 11 Starting doses of larotrectinib (PIP03 SAF)

	HGG N=22	LGG N=13	Non-glioma N=5	Total PIP03 SAF N=40
Actual dose, mg BID				
Median	75.50	100.00	100.00	82.00
Range	12.0, 100.0	60.0, 150.0	92.0, 100.0	12.0, 150.0
Actual dose, mg/m^2 BID				
Median	99.85	98.77	72.00	98.87
Range	24.4, 109.7	63.5, 112.8	52.2, 99.7	24.4, 112.8

BID = twice daily; HGG = high-grade glioma; LGG = low-grade glioma; N = total number of patients (100%); PIP03 = pediatric investigation plan 03; SAF = Safety analysis set

There were no DLTs reported in the paediatric PIP03 SAF population of Study 20290.

Table 12 Larotrectinib study treatment duration (PIP03 SAF)

	HGG N=22	LGG N=13	Non-glioma N=5	Total PIP03 SAF N=40
Time on treatment (months) [a]				
Median	20.15	23.00	18.30	20.80
Range	1.2, 65.2	2.5, 64.9	14.9, 22.3	1.2, 65.2
Cycles initiated [b]				
Median	22.0	25.0	20.0	23.0
Range	2, 72	3, 71	15, 24	2, 72
Patients with any dose missed, skipped, or delayed, n (%)	20 (91)	13 (100)	5 (100)	38 (95)
Patients with any dose reduction, n (%)	11 (50)	6 (46)	1 (20)	18 (45)

HGG = high-grade glioma; LGG = low-grade glioma; N = total number of patients (100%); n = number of patients within category; PIP03 = pediatric investigational plan 03; SAF = Safety analysis set
Percentages are based on the number of patients (N) specified in the column header.
[a] Time on treatment = (first date of last cycle + 28 days – first dose date + 1)/30.4375. Includes any time off drug and in wait and see periods.
[b] Planned cycle length was 28 days.

Study treatment duration ≤2 years was reported for 26 (65%) of the patients vs. duration >2 years for 14 (35%) of the patients in the PIP03 population.

In the HGG subgroup, 14/22 (64%) patients were on study treatment ≤2 years vs. 8/22 (36%) >2 years. In the LGG subgroup, the corresponding numbers were 7/13 ≤2 years vs. 6/13 (46%) >2 years. In the non-glioma subgroup, all five patients were on study treatment ≤2 years.

Table 13 Study drug dosage modifications by treatment period (SAF)

Treatment Epoch: Overall duration of treatment

	HGG N=22 (100%)	LGG N=13 (100%)	Non-Glioma N=5 (100%)	Total N=40 (100%)
Any Dose Modification				
Yes	20 (91%)	13 (100%)	5 (100%)	38 (95%)
Dose Modification Event [1]				
Dose Increased	16 (73%)	7 (54%)	2 (40%)	25 (63%)
Adverse event	1 (5%)	0	0	1 (3%)
Other reason	16 (73%)	6 (46%)	2 (40%)	24 (60%)
Pharmacokinetics	1 (5%)	0	0	1 (3%)
Protocol violation	1 (5%)	1 (8%)	0	2 (5%)
Dose Missed/Skipped/Delayed	20 (91%)	13 (100%)	5 (100%)	38 (95%)
Adverse event	9 (41%)	5 (38%)	2 (40%)	16 (40%)
Other reason	17 (77%)	11 (85%)	5 (100%)	33 (83%)
Pharmacokinetics	0	0	0	0
Protocol violation	1 (5%)	2 (15%)	0	3 (8%)
Dose Reduced	11 (50%)	6 (46%)	1 (20%)	18 (45%)
Adverse event	1 (5%)	2 (15%)	0	3 (8%)
Other reason	10 (45%)	5 (38%)	1 (20%)	16 (40%)
Pharmacokinetics	1 (5%)	0	0	1 (3%)
Protocol violation	1 (5%)	0	0	1 (3%)

[1] Patients may be counted in more than one row
Percentages are based on the N specified in the column header

Dose increase was reported for 25/40 (63%) of the PIP03 population. The most common reason for dose increase was `other reason´, including change in body surface area, PK modelling results (in line with the study protocol's original dosing paradigm), protocol violation, and AE (vomiting requiring an additional dose).

Adverse events overview

All AEs arising or worsening after start of study drug administration were defined as TEAEs, regardless of whether they started in a `wait and see period´, after successful resection surgery, or in active safety follow up.

Table 14 Overall adverse event summary (PIP03 SAF)

	Patient incidence, n (%)			
Category of TEAE	**HGG N=22**	**LGG N=13**	**Non-glioma N=5**	**Total PIP03 SAF N=40**
Any TEAE				
All	22 (100)	13 (100)	5 (100)	40 (100)
Related to larotrectinib	11 (50)	9 (69)	5 (100)	25 (63)
Grade 3, 4, or 5 TEAE [a]				
All	17 (77)	6 (46)	2 (40)	25 (63)
Related to larotrectinib	4 (18)	1 (8)	1 (20)	6 (15)
TEAEs resulting in larotrectinib permanent discontinuation				
All	3 (14)	1 (8)	1 (20)	5 (13)
Related to larotrectinib	0	0	0	0
Serious TEAE				
All	15 (68)	6 (46)	3 (60)	24 (60)
Related to larotrectinib	2 (9)	0	1 (20)	3 (8)
TEAEs considered DLT	0	0	0	0
Fatal TEAE (Grade 5) [a]				
All	2 (9)	1 (8)	0	3 (8)
Related to larotrectinib	0	0	0	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; HGG = high-grade glioma; LGG = low-grade glioma; N = total number of patients (100%); n = number of patients within category; PIP03 = pediatric investigational plan 03; SAF = Safety analysis set; TEAE = treatment-emergent adverse event

Percentages are based on the number of patients (N) specified in the column header.

[a] Severity grade assessment based on CTCAE (version 4.03): Grade 3 (severe), Grade 4 (life-threatening), Grade 5 (death).

As multiple treatment periods could occur when surgical resection patients and patients in a wait and see period restarted larotrectinib treatment following disease recurrence or progressive disease (PD), a sensitivity analysis of TEAEs was performed looking only at TEAEs that occurred <28 days of any

larotrectinib treatment. The number of patients with TEAEs in this sensitivity analysis were the same as the overall number of patients with TEAEs presented in the table above.

Post-treatment AEs, defined as any AE arising or worsening >28 days after the end of a larotrectinib treatment period, were reported in seven (18%) of the PIP03 patients. Of these, two (5%) were grade ≥3 and none were serious. According to the investigator, none of the post-treatment AEs were considered related to the larotrectinib treatment.

Adverse events by SOC and PT

Table 15 Adverse events by system organ class (PIP03)

	Patient incidence, n (%)			
SOC	HGG N=22	LGG N=13	Non-glioma N=5	Total PIP03 SAF N=40
Any TEAE				
Infections and infestations	19 (86)	12 (92)	2 (40)	33 (83)
Gastrointestinal disorders	16 (73)	11 (85)	2 (40)	29 (73)
General disorders and administration site conditions	15 (68)	8 (62)	3 (60)	26 (65)
Nervous system disorders	12 (55)	9 (69)	4 (80)	25 (63)
Investigations	13 (59)	7 (54)	4 (80)	24 (60)
Respiratory, thoracic and mediastinal disorders	14 (64)	7 (54)	0	21 (53)
Skin and subcutaneous tissue disorders	9 (41)	7 (54)	2 (40)	18 (45)
Metabolism and nutrition disorders	10 (45)	6 (46)	0	16 (40)
Injury, poisoning and procedural complications	7 (32)	8 (62)	0	15 (38)
Blood and lymphatic system disorders	6 (27)	5 (38)	1 (20)	12 (30)
Musculoskeletal and connective tissue disorders	6 (27)	4 (31)	1 (20)	11 (28)
Psychiatric disorders	4 (18)	4 (31)	1 (20)	9 (23)
Ear and labyrinth disorders	3 (14)	3 (23)	1 (20)	7 (18)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (9)	4 (31)	0	6 (15)
Renal and urinary disorders	3 (14)	2 (15)	1 (20)	6 (15)
Endocrine disorders	3 (14)	2 (15)	0	5 (13)
Vascular disorders	2 (9)	2 (15)	1 (20)	5 (13)
Eye disorders	1 (5)	2 (15)	0	3 (8)
Cardiac disorders	1 (5)	1 (8)	0	2 (5)
Immune system disorders	2 (9)	0	0	2 (5)
Congenital, familial and genetic disorders	1 (5)	0	0	1 (3)
Hepatobiliary disorders	0	1 (8)	0	1 (3)
Not coded	0	1 (8)	0	1 (3)
Surgical and medical procedures	1 (5)	0	0	1 (3)

AE = adverse event; HGG = high-grade glioma; LGG = low-grade glioma; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients (100%); n = number of patients within category; PIP03 = pediatric investigational plan 03; SAF = Safety analysis set; SOC = system organ class; TEAE = treatment-emergent adverse event

Patients were counted once within each SOC.

Reported AE terms were coded using MedDRA dictionary (Version 26.0).

Percentages are based on the number of patients (N) specified in the column header.

Table 16 Treatment-emergent adverse events by preferred term (with overall incidence of >20% of patients) (PIP03 SAF)

	Patient incidence, n (%)			
Preferred term	HGG N=22	LGG N=13	Non-glioma N=5	Total PIP03 SAF N=40
Any TEAE	22 (100)	13 (100)	5 (100)	40 (100)
Vomiting	9 (41)	8 (62)	1 (20)	18 (45)
Pyrexia	11 (50)	4 (31)	0	15 (38)
ALT increased	7 (32)	5 (38)	2 (40)	14 (35)
Cough	9 (41)	5 (38)	0	14 (35)
Upper respiratory tract infection	9 (41)	5 (38)	0	14 (35)
AST increased	8 (36)	3 (23)	2 (40)	13 (33)
Diarrhoea	10 (45)	2 (15)	0	12 (30)
Headache	3 (14)	6 (46)	2 (40)	11 (28)
Neutrophil count decreased [a]	3 (14)	5 (38)	1 (20)	9 (23)
Constipation	6 (27)	2 (15)	0	8 (20)
Nasopharyngitis	4 (18)	4 (31)	0	8 (20)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HGG = high-grade glioma; LGG = low-grade glioma; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients (100%); n = number of patients within category; PIP03 = pediatric investigational plan 03; SAF = Safety analysis set; TEAE = treatment-emergent adverse event

Patients are counted once within each preferred term.

Reported AE terms were coded using MedDRA dictionary (Version 26.0).

Percentages are based on the total number of patients (N) specified in the column header.

[a] Medical term Neutrophil count decreased includes the MedDRA preferred terms Neutrophil count decreased and Neutropenia.

Post-treatment AEs, defined as any AE arising or worsening >28 days after the end of a larotrectinib treatment period, were reported in seven (18%) of the PIP03 patients. Of these, two (5%) were grade ≥3 and none were serious. According to the investigator, none of the post-treatment AEs were considered related to the larotrectinib treatment.

Adverse events by severity

Table 17 Grade ≥3 adverse events considered related to larotrectinib or with overall incidence of more than one patient (PIP03 SAF)

	All patients, n (%) N = 40	
Preferred term	All TEAEs	Larotrectinib-related TEAEs
Any Grade ≥3 TEAE	25 (63)	6 (15)
Neutrophil count decreased [a]	4 (10)	3 (8)
Headache	3 (8)	0
Gamma-glutamyltransferase increased	2 (5)	2 (5)
Hyperglycaemia	2 (5)	1 (3)
Balance disorder, Diarrhoea, Dysphagia, Hydrocephalus, Pneumonia, Vomiting	2 each (5)	
Larotrectinib-related TEAEs: ALT increased, Hypernatraemia, Hyponatraemia	[b]	1 each (3)

AE = adverse event; ALT = alanine aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients (100%); n = number of patients within category; SAF = Safety analysis set; TEAE = treatment-emergent adverse event

Patients are counted once within each preferred term.

Reported AE terms were coded using MedDRA dictionary (Version 26.0).

Percentages are based on the number of patients (N) specified in the column header.

[a] Medical term Neutrophil count decreased includes the MedDRA preferred terms Neutrophil count decreased and Neutropenia.

Treatment-related adverse events

Table 18 Larotrectinib-related adverse events with overall incidence of ≥10% (PIP03 SAF)

	Patient incidence, n (%)			
Preferred term	HGG N=22	LGG N=13	Non-glioma N=5	Total PIP03 SAF N=40
Any larotrectinib-related TEAE	**11 (50)**	**9 (69)**	**5 (100)**	**25 (63)**
ALT increased	5 (23)	5 (38)	2 (40)	12 (30)
AST increased	6 (27)	1 (8)	1 (20)	8 (20)
Neutrophil count decreased	3 (14)	4 (31)	1 (20)	8 (20)
Leukocyte count decreased	3 (14)	1 (8)	0	4 (10)
Anaemia	2 (9)	2 (15)	0	4 (10)
Vomiting	1 (5)	3 (23)	0	4 (10)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HGG = high-grade glioma; LGG = low-grade glioma; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients (100%); n = number of patients within category; PIP03 = pediatric investigational plan 03; SAF = Safety analysis set; TEAE = treatment-emergent adverse event; WBC = white blood cell

Patients are counted once within each preferred term.

Reported AE event terms were coded using MedDRA dictionary (Version 26.0).

Percentages are based on the number of patients (N) specified in the column header.

[a] Medical term 'neutrophil count decreased' includes the MedDRA preferred terms neutrophil count decreased, and neutropenia.

[b] Medical term 'leukocyte count decreased' includes the MedDRA preferred terms leukocyte count decreased, leukopenia, and WBC count decreased.

Adverse events by age

Table 19 Overall adverse event summary by age group (PIP03 SAF)

	Patient Incidence, n (%)			
Category of TEAE	Infants and toddlers: birth to <24 months N=4	Children: 2 to <12 years N=32	Adolescent: 12 to <18 years N=4	Total PIP03 SAF N=40
Any TEAE				
All	4 (100)	32 (100)	4 (100)	40 (100)
Related to larotrectinib	1 (25)	20 (63)	4 (100)	25 (63)
Grade ≥3 TEAE [a]				
All	4 (100)	19 (59)	2 (50)	25 (63)
Related to larotrectinib	0	6 (19)	0	6 (15)
TEAEs resulting in larotrectinib permanent discontinuation				
All	1 (25)	3 (9)	1 (25)	5 (13)
Related to larotrectinib	0	0	0	0
Serious TEAE				
All	4 (100)	17 (53)	3 (75)	24 (60)
Related to larotrectinib	0	3 (9)	0	3 (8)
TEAEs considered DLT	0	0	0	0
Fatal TEAE (Grade 5) [a]				
All	1 (25)	2 (6)	0	3 (8)
Related to larotrectinib	0	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; N = total number of patients (100%); n = number of patients within category; SAF = Safety analysis set; TEAE = treatment-emergent adverse event

Percentages are based on the number of patients (N) specified in the column header.

[a] Severity grade assignment based on CTCAE (version 4.03): Grade 3 (severe), Grade 4 (life-threatening), Grade 5 (death).

Table 20 Common adverse events by age group (with incidence of >20% in any age group) and relationship to larotrectinib (PIP03 SAF)

	Patient Incidence, n (%)					
	Infants and toddlers: birth to <24 months N=4		Children: 2 to <12 years N=32		Adolescents: 12 to <18 years N=4	
	TEAE	Related	TEAE	Related	TEAE	Related
Any TEAE	4 (100)	1 (25)	32 (100)	20 (63)	4 (100)	4 (100)
Headache	0	0	9 (28)	2 (6)	2 (50)	0
Abdominal pain	0	0	4 (13)	0	1 (25)	1 (25)
Asthenia	0	0	1 (3)	0	1 (25)	1 (25)
Blood alkaline phosphatase increased	0	0	4 (13)	1 (3)	1 (25)	1 (25)
Blood creatinine increased	0	0	3 (9)	0	1 (25)	1 (25)
Depressed level of consciousness	0	0	2 (6)	0	1 (25)	0
Disturbance in attention	0	0	2 (6)	0	1 (25)	0
Dizziness	0	0	2 (6)	0	1 (25)	0
Electrocardiogram T wave inversion	0	0	0	0	1 (25)	0
Erythema	0	0	0	0	1 (25)	0
Fatigue	2 (50)	0	4 (13)	1 (3)	1 (25)	0
Gait disturbance	0	0	2 (6)	0	1 (25)	0
Granuloma	0	0	0	0	1 (25)	0
Hallucination	0	0	0	0	1 (25)	1 (25)
Hot flush	0	0	0	0	1 (25)	1 (25)
Metabolic acidosis	0	0	0	0	1 (25)	0
Motor dysfunction	0	0	0	0	1 (25)	0
Musculoskeletal chest pain	0	0	0	0	1 (25)	0
Nasopharyngitis	1 (25)	0	6 (19)	0	1 (25)	0
Presyncope	0	0	0	0	1 (25)	0
Rash	3 (75)	0	2 (6)	0	1 (25)	1 (25)
Seizure	1 (25)	0	0	0	1 (25)	0
Skin infection	1 (25)	0	2 (6)	0	1 (25)	0
Tremor	0	0	1 (3)	0	1 (25)	0
Vomiting	2 (50)	0	15 (47)	4 (13)	1 (25)	0
Weight increased	0	0	2 (6)	2 (6)	1 (25)	1 (25)
ALT increased	0	0	14 (44)	12 (38)	0	0
Anaemia	1 (25)	0	4 (13)	4 (13)	0	0
AST increased	0	0	13 (41)	8 (25)	0	0
COVID-19	1 (25)	0	6 (19)	0	0	0
Conjunctivitis	1 (25)	0	6 (19)	0	0	0
Constipation	1 (25)	0	7 (22)	1 (3)	0	0
Contusion	1 (25)	0	3 (9)	0	0	0
Cough	1 (25)	0	13 (41)	1 (3)	0	0
Decreased appetite	1 (25)	0	3 (9)	1 (3)	0	0
Dermatitis diaper	2 (50)	0	0	0	0	0
Device related infection	1 (25)	0	0	0	0	0
Diarrhoea	2 (50)	0	10 (31)	1 (3)	0	0
Dry skin	1 (25)	0	3 (9)	0	0	0
Epistaxis	1 (25)	0	1 (3)	0	0	0
Eye infection	1 (25)	0	0	0	0	0
Febrile convulsion	1 (25)	0	0	0	0	0
Hyperthermia	1 (25)	0	0	0	0	0
Hypotension	1 (25)	0	2 (6)	0	0	0
Influenza	1 (25)	0	1 (3)	0	0	0
Influenza like illness	1 (25)	0	4 (13)	0	0	0
Irritability	1 (25)	0	1 (3)	1 (3)	0	0
Malignant neoplasm progression	1 (25)	0	0	0	0	0
Miliaria	1 (25)	0	0	0	0	0
Nail infection	1 (25)	0	0	0	0	0
Nasal congestion	2 (50)	0	3 (9)	0	0	0
Nausea	1 (25)	1 (25)	3 (9)	1 (3)	0	0
Neutrophil count decreased [a]	0	0	9 (28)	8 (25)	0	0
Pain	1 (25)	0	0	0	0	0
Pneumonia	1 (25)	0	3 (9)	0	0	0
Pneumonitis	1 (25)	0	0	0	0	0
Postictal paralysis	1 (25)	0	0	0	0	0
Pyrexia	3 (75)	0	12 (38)	0	0	0
Rhinorrhoea	2 (50)	0	3 (9)	0	0	0
Teething	1 (25)	0	0	0	0	0
Upper respiratory tract congestion	1 (25)	0	0	0	0	0
Upper respiratory tract infection	2 (50)	0	12 (38)	0	0	0
Urinary tract infection	1 (25)	0	4 (13)	1 (3)	0	0
Viral infection	1 (25)	0	5 (16)	0	0	0

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients (100%); n = number of patients within category; SAF = Safety analysis set; TEAE = treatment-emergent adverse event

Patients are counted once within each preferred term.

Reported AE terms were coded using MedDRA dictionary (version 26.0).

Percentages are based on the number of patients (N) specified in the column header.

[a] Medical term neutrophil count decreased includes the MedDRA preferred terms neutrophil count decreased and neutropenia.

Due to the small sample size in the infants and toddlers and adolescent subgroups (n=4 each), a comparison of the TEAE profile between the age groups was difficult.

Serious adverse events

A total of 55 SAEs, regardless of considered related to larotrectinib or not, were reported in the PIP03 population. Most of SAEs occurred in the HGG subgroup, of which hyperglycaemia (n=5) was the most frequently occurring.

More than one SAE was reported for eight patients, with three of these patients having more than three SAEs. The SAEs were mostly grade 2 or 3 but ranged from grade 1 (mild) to 5 (fatal).

At the DCO, four patients had SAEs that were ongoing. One unresolved SAE event led to larotrectinib discontinuation (PT motor dysfunction).

Table 21 Serous adverse events considered related to larotrectinib or with overall incidence of more than one patient (PIP03 SAF)

	All patients, n (%) N = 40	
Preferred term	Any SAEs	Larotrectinib-related SAEs
Any SAE	24 (60)	3 (8)
Headache	3 (8)	1 (3)
Influenza, Pneumonia, Urinary tract infection, Vomiting	2 each (5)	0
Hyperglycaemia	2 (5)	1 (3)
Hypernatraemia, Hyponatraemia	1 each (3)	1 each (3)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients (100%); n = number of patients within category; PIP03 = pediatric investigational plan 03; SAE = serious adverse event; SAF = Safety analysis set
Patients were counted once within each preferred term.
Reported AE terms were coded using MedDRA dictionary version 26.0.
Percentages are based on the number of patients (N) specified in the column header.

Deaths

As of the DCO, 10 patients in the PIP03 SAF had died, including eight patients with HGG, one patient with LGG, and one patient with non-glioma.

Three patients in the SAF died within 28 days of their last dose of larotrectinib (two with HGG, one with LGG. According to the investigator, none of these three events were considered related to larotrectinib. For one of the HGG patients, the primary cause of death was an AE (not otherwise specified) other than disease progression. The other two patients died due to disease progression (one HGG patient died due to PT glioblastoma multiforme and one LGG patient died due to PT malignant neoplasm progression).

A total of seven patients died >28 days after their last dose of larotrectinib, including six with HGG, and one patient with non-glioma. The primary cause of death was disease progression for six patients (five with HGG, one with non-glioma) and an AE (other than disease progression and not otherwise specified) for one HGG patient.

Adverse events leading to treatment modification

Dose interruptions and reductions for management of toxicities as well as dose re-escalation were allowed. No dose escalation above 100 mg BID was permitted.

Table 22 Treatment-emergent adverse events with action taken of study drug interrupted (SAF)

Preferred Term	HGG N=22 (100%)	LGG N=13 (100%)	Non-Glioma N=5 (100%)	Total N=40 (100%)
Patients with TEAE	8 (36%)	5 (38%)	1 (20%)	14 (35%)
Neutrophil count decreased	1 (5%)	1 (8%)	0	2 (5%)
Alanine aminotransferase increased	0	1 (8%)	0	1 (3%)
Blepharoplasty	1 (5%)	0	0	1 (3%)
Bronchitis	1 (5%)	0	0	1 (3%)
Device related infection	0	1 (8%)	0	1 (3%)
Gamma-glutamyltransferase increased	0	0	1 (20%)	1 (3%)
Hepatic function abnormal	0	1 (8%)	0	1 (3%)
Hyperglycaemia	1 (5%)	0	0	1 (3%)
Hypernatraemia	1 (5%)	0	0	1 (3%)
Hyponatraemia	1 (5%)	0	0	1 (3%)
Pneumonia	1 (5%)	0	0	1 (3%)
Pneumonitis	1 (5%)	0	0	1 (3%)
Pyogenic granuloma	0	1 (8%)	0	1 (3%)
Pyrexia	1 (5%)	0	0	1 (3%)
Somnolence	0	1 (8%)	0	1 (3%)
Upper respiratory tract infection	1 (5%)	0	0	1 (3%)
Urinary tract infection	1 (5%)	0	0	1 (3%)

Patients are counted once within each preferred term.
Reported adverse event terms were coded using MedDRA dictionary (version 26.0).
Adverse events are sorted in decreasing order of frequency based on the total column.

Table 23 Overview of dose modifications in subjects having TEAEs that lead to dose interruptions (SAF)

	HGG N=22 (100%)	LGG N=13 (100%)	Non-Glioma N=5 (100%)	Total N=40 (100%)
Any Dose interruptions due to TEAE (based on adverse event dataset)				
YES	8 (36%)	5 (38%)	1 (20%)	14 (35%)
Study Drug Modifications due to TEAE (based on exposure dataset) [1]				
Dose Delayed	1 (5%)	0	0	1 (3%)
Dose Increased	1 (5%)	0	0	1 (3%)
Dose Missed/Skipped	8 (36%)	5 (38%)	1 (20%)	14 (35%)
Dose Reduced	1 (5%)	2 (15%)	0	3 (8%)
Dose Resumed	1 (5%)	0	0	1 (3%)

[1] Patients may be counted in more than one row.
Percentages are based on the N specified in the column header.

One patient in the SAF had a dose increase due to weight increase.

Adverse events leading to treatment discontinuation

A total of five (13%) patients discontinued larotrectinib due to a TEAE, including three patients with HGG, one with LGG, and one with non-glioma. According to the investigator, none of these events were considered related to larotrectinib.

Table 24 Treatment-emergent adverse events with study drug permanently discontinued (SAF)

Preferred Term	HGG N=22 (100%)	LGG N=13 (100%)	Non-Glioma N=5 (100%)	Total N=40 (100%)
Patients with TEAE	3 (14%)	1 (8%)	1 (20%)	5 (13%)
Dysarthria	1 (5%)	0	0	1 (3%)
Glioblastoma multiforme	1 (5%)	0	0	1 (3%)
Glioma	1 (5%)	0	0	1 (3%)
Malignant neoplasm progression	0	1 (8%)	0	1 (3%)
Motor dysfunction	0	0	1 (20%)	1 (3%)

Patients are counted once within each preferred term.
Reported adverse event terms were coded using MedDRA dictionary (version 26.0).
Adverse events are sorted in decreasing order of frequency based on the total column.

The TEAE dysarthria was a grade 3 TEAE, the TEAE motor dysfunction was reported as a grade 2 SAE, and the TEAE glioma was a grade 3 SAE. The TEAEs glioblastoma multiforme and TEAE progressive disease were grade 5 SAEs.

Adverse events of special interest

Adverse events of special interest (AESI) were identified based on predictions from the TRK-related neurobiology literature, the preclinical toxicology program, and primarily, clinical experience with larotrectinib. The following AESIs were identified:

- ALT and AST elevation
- neurologic events (including peripheral neuropathy and impaired neurodevelopment in paediatric patients)
- neutropenia and febrile neutropenia
- drug withdrawal pain syndrome
- fracture events.

ALT and AST elevations

A total of 15 (38%) patients had TEAEs of ALT and/or AST increased, of which nine were grade 1, five grade 2, and one grade 3. One patient had the larotrectinib dose interrupted due to grade 3 ALT and/or AST increased.

No patients met the Hy's Law definition of drug induced liver injury.

Neurologic events

In the postnatal period, TRK receptors are expressed in the brain and nervous system and are thought to regulate mood, memory, cognition, and proprioception (Snider 1994). To examine the possible clinical manifestations of neurologic toxicity by TRK inhibition, the incidence rates of preferred terms from the system organ class (SOC) 'Nervous system disorders', and SOC 'Psychiatric disorders' were extracted from TEAE output as well as the preferred term (PT) of 'Gait disturbance' coded under the primary SOC 'General disorders and administration site conditions´, and the secondary SOC 'Nervous system disorder´.

The reported neurologic events were grade 1-3. There were no fatal neurologic events.

Two patients had neurologic events that led to permanent discontinuation of larotrectinib (grade 2 TEAE of motor dysfunction and grade 3 TEAE of dysarthria). One patient had neurologic events that led to study treatment interruption (grade 1 TEAE of somnolence). According to the investigator, these TEAEs were not considered related to larotrectinib.

Table 25 Neurologic events in ≥1 patient overall (PIP03 SAF)

SOC Preferred term	Patient incidence, n (%) Any AE N=40	Any larotrectinib-related AE of worst Grade ≤2 N=40	Any larotrectinib-related AE of worst Grade ≥3 N=40
Any neurologic event	26 (65)	5 (13)	0
General disorders and administration site conditions	3 (8)	0	0
Gait disturbance	3 (8)	0	0
Nervous system disorders	25 (63)	3 (8)	0
Headache	11 (28)	2 (5)	0
Ataxia	3 (8)	0	0
Balance disorder	3 (8)	0	0
Depressed level of consciousness	3 (8)	0	0
Disturbance in attention	3 (8)	0	0
Dizziness	3 (8)	0	0
Hemiparesis	3 (8)	0	0
Memory impairment	3 (8)	1 (3)	0
Somnolence	3 (8)	0	0
Dysgeusia	2 (5)	2 (5)	0
Facial paralysis	2 (5)	0	0
Hydrocephalus	2 (5)	0	0
[illegible] araesthesia	2 (5)	1 (3)	0
[illegible] artial seizures	2 (5)	0	0
Seizure	2 (5)	0	0
Tre[illegible]or	2 (5)	0	0
[illegible]sychiatric disorders	[illegible] (23,	3 (8)	0
Insomnia	3 (8)	0	0
An[illegible]iety	2 (5)	1 (3)	0
Enuresis	2 (5)	0	0
Irritability	2 (5)	1 (3)	0
Agitation	1 (3)	1 (3)	0
Attention deficit hyperactivity disorder	1 (3)	0	0
Hallucination	1 (3)	1 (3)	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients (100%); n = number of patients within category; PT = preferred term; SAF = Safety analysis set; SOC = system organ class

Table includes PTs from the Nervous System Disorders and Psychiatric Disorders SOCs that represent neurologic events of special interest. The PT of 'Gait disturbance' is included as a neurologic event in the safety analyses being coded under the primary SOC General disorders and administration site conditions and the secondary SOC Nervous system disorders.

Patients with multiple severity ratings for a given AE are counted once under the maximum severity.

Reported AE terms were coded using MedDRA dictionary version 26.0.

Severity grade assignment based on CTCAE (v4.03): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening); Grade 5 (fatal).

Percentages are based on the number of patients (N) specified in the column header.

Neutropenia/febrile neutropenia

A total of nine (23%) of the patients were reported to have TEAEs neutropenia. Of these, three were grade 1, two were grade 2, and four were grade 3. Two patients interrupted larotrectinib treatment due to TEAE neutropenia, but no had dose reductions or discontinued larotrectinib. Of the TEAE neutropenia cases, eight were considered related to larotrectinib according to the investigator.

There were no reports of TEAE febrile neutropenia.

Drug withdrawal pain syndrome

Withdrawal pain (discontinuation syndrome) has been described in patients receiving TRK inhibitors after temporarily or permanently discontinuing treatment (Liu et al. 2020). Symptoms have been described as full-body ache, muscle pain, and/or allodynia, occasionally accompanied by a headache.

There were two patients in the PIP03 SAF who experienced at least one event of drug withdrawal pain (no details presented).

Fracture events

Evaluation of skeletal fractures was conducted by cumulatively reviewing the clinical databases to identify all events of fractures reported in patients treated with larotrectinib, using the term 'fracture' as a search keyword in the preferred term(s).

A total of three patients (one with HGG, two with LGG) reported a TEAE of fracture. These were tooth fracture (grade 1), upper limb fracture (grade 2), and wrist fracture (grade 2). All TEAEs of fracture resolved without sequelae. According to the investigator, TEAEs fracture were not related to larotrectinib treatment.

The median time to first fracture event was 6.9 months (range 2.3 to 49.5 months) and the mean time was 19.6 months (standard deviation 26.0).

Clinical laboratory evaluation

All clinical chemistry values are reported using the Common Terminology Criteria for Adverse Events (CTCAE).

Haematology

At baseline, most patients had normal haematology values (i.e., grade 0). There were eight (20%) patients with grade 1 and three (8%) with grade 2 haemoglobin decreased at baseline vs. two (5%) with platelet count decreased grade 1, and eight (20%) patients with grade 1 and one (3%) with grade 2 with white blood cell (WBC) count decreased at baseline.

The changes seen in total WBC count were due primarily to changes in neutrophils.

Median values for maximum decrease from baseline in laboratory value was -11.0 g/L (min, max -36, 11) for haemoglobin, -52.5 $x10^9$/L (min, max -334, 42) for platelet count , -2.0.0 $x10^9$/L (min, max -6, 1) for WBC count, and -1.3 x.0 10^9/L (min, max -5, 1) for neutrophil count, respectively.

Clinical chemistry

Serum chemistry parameters with significant changes from baseline were ALT, AST, bilirubin, and ALP increased, albumin decreased, and LDH increased.

At baseline, all but one (3%) patient (grade 1 ALT increased) had normal ALT levels. At last post-baseline evaluation, 10 (25%) had grade 1, two (5%) had grade 2, and one (3%) had grade 3 ALT increased. The remaining 27 (68%) patients had normal ALT levels. The maximum ALT reported was 454 U/L (grade 3, one patient).

At baseline, all but one (3%) patient (grade 1 AST increased) had normal AST levels. At last post-baseline evaluation, 12 (30%) had grade 1, and one (3%) had grade 2 AST increased. The remaining 27 (68%) had normal AST levels post-baseline. The maximum reported AST was 744 U/L (grade 3, the same patient that had the maximum ALT value).

All but one (3%) patient (grade 1 bilirubin increased) had normal bilirubin levels at baseline. At last post-baseline evaluation all patients had normal bilirubin levels.

All but two (5%) patients (one grade 1 and one grade 2 ALP increased) had normal ALP levels at baseline. At last post-baseline evaluation, two (5%) patients had grade 1 ALP increased and the other 38 (95%) patients had normal ALP levels.

At baseline, 37 (93%) of the patients had normal albumin levels. One (3%) patient had a grade 1 albumin decrease and one (3%) a grade 3 albumin decreased. Data were missing for one (3%) patient

at baseline. At last post-baseline evaluation, 10 (25%) had grade 1 and one (3%) had grade 2 albumin decreased. The remaining 29 /(73%) patients had normal albumin levels post-baseline.

Changes in LDH were reported as normal, below lower limit of normal (LLN) and above upper limit of normal (ULN), since no CTCAE grades for LDH shifts exist. At baseline, 27 (68%) patients had normal and 12 (30%) values below LLN and above ULN (six [15%] each). Data were missing for one (3%) patient at baseline. At the last post-baseline evaluation, 20 (50%) patients had LDH values within the normal range, seven (8%) below LLN, and 13 (33%) above ULN.

Other safety variables

There were no clinically significant treatment-emergent trends in impact on vital signs, developmental growth.

For all children, symptom-directed neurological examinations were used to identify profound changes in behaviour or cognitive development. Assessments were performed throughout the study with symptoms that were new or worsened in severity reported as TEAEs. Relation to larotrectinib was not recorded for neurological examinations.

Neurological symptoms

Overall, 29 patients (73%) in the PIP03 SAF experienced at least one neurological symptom. Of these, 15 (38%) patients had CTCAE grade 1 symptoms, 8 (20%) had CTCAE grade 2, and 6 (15%) had CTCAE grade 3 symptoms while on treatment (five patients had a grade 3 neurological symptom at screening). The only grade 3 symptoms occurring ≥2 patients overall were ataxia and cognitive disturbance (three [8%] patients each). No patients reported neurological symptoms of grade 4 or 5.

Neurocognitive developmental progress

The Ages & Stages questionnaire, 3rd edition (ASQ3 questionnaire), a screening tool to monitor neurocognitive developmental progress in children between the ages of one month to 5.5 years, was implemented in Study 20290 in April 2020 (study protocol amendment version 12.0). Questionnaires applicable to the patients' age were to be collected at age specific time points up until 66 months of age (including during wait and see periods, after resection surgery resulting in negative margins, and active safety follow-up). The questionnaire was administered at baseline for newly enrolled patients and every 6 months thereafter.

The ASQ3 questionnaire comprises five domain areas: communication, gross motor, fine motor, problem solving, and personal-social. Each domain area comprises six questions and parent rate the most appropriate answer as to the presence of each skill, `Yes´, `Sometimes´, `Not Yet´, with point values of 10, 5, or 0, respectively. Each domain question set is totalled independently by the investigator and categorized (based on their total score) into an overall domain assessment of 'well above', 'monitor' (score was 1 to 2 standard deviations below the mean), or 'below' (score was >2 standard deviations below the mean). An overall interpretation of normal or abnormal for age is also provided by the investigator.

Eleven patients, ranging from 1 month to 4 years of age, completed the ASQ3 questionnaire. Eight patients provided ASQ score for all 5 domains for 4-8 time periods and three patients only provided 1 or 2 ASQ scores. Across the span of neurocognitive development as reported by parents and scored independently over time, all patients neurocognitive development scores were normal for age by investigator at DCO. The data indicate that neurocognitive development milestones are not at risk in these patients.

2.3.3.3.8. Safety of the new oral solution

The palatability analysis set (n=17) was used for the assessment of safety of the new 2% oral solution in the PIP03 Report.

At the DCO (18 May 2024), the patients in the palatability analysis set had initiated a median of 19.0 larotrectinib cycles (range 3 to 56), with a median study treatment duration of 18.20 months (range 2.5 to 51.4).

All patients in the palatability analysis set experienced at least one TEAE, with the most common TEAEs (>40% of patients) being AST increased (59%), ALT increased and pyrexia (53% each), and upper respiratory tract infection and vomiting (47% each).

According to the investigator, there were 12 patients (71%) with TEAEs related to larotrectinib and 13 patients (76%) with TEAEs that were of worst grade ≥3.

There were two patients (12%) with grade 5 TEAEs and altogether four patients in the palatability analysis set had died at the DCO. Serious TEAEs were reported in 11 patients (65%).

2.3.3.3.9. Safety in the pooled adult and paediatric population

Data of the pooled adult and paediatric population are reported in the 5th annual renewal analysis, with DCO date 20 Jul 2023.

2.3.3.4. Pharmacokinetics

All 40 patients' data were included in the data analysis set and had had sufficient post-dose samples to be included in the PK analysis set table 26.

Table 26 Summary of Data and PK Analysis Sets

Study Phase	Pediatric Age Group	Number of Patients	
		Cycle 1 Day 1 N= 40	Cycle 4 Day 1 N= 37
Phase 1 Dose Expansion	2 to < 6 years	5	4
	6 to < 12 years	3	3
	12 to < 18 years	3	3
Phase 2 Cohort 3	1 to 3 months	1	1
	1 to < 2 years	3	2
	2 to < 6 years	10	10
	6 to < 12 years	14	13
	12 to < 18 years	1	1

The initial starting dose level in the phase 1 portion was based on a dose i.e., 100 mg BID in adults, and PK modelling (SimCyp®) was used to select a dose for paediatric patients that was predicted to equal the exposure achieved in adult patients taking a dose of 100 mg BID. The modelling took into account the differences in the body size and ontogeny of the enzymes that metabolized larotrectinib. The doses given in phase 1 dose expansion cohort were 98.7 to 112 mg/m^2 in the 2-6 years paediatric age group and 64.5 to 104 mg/m^2 in other paediatric age groups. The RP2D was 100 mg/m^2 BID, not to exceed a dose of 100 mg BID. The phase 2 posology is in accordance with the approved SmPC. For this reason, PK results from phase 2 cohort 3 are presented.

A summary of plasma larotrectinib PK parameters are presented in Table 27 for cycle 1 day 1 and in Table 28 for cycle 4 day 1, and the mean plasma concentration of larotrectinib over time for cycle 4 day 1 is presented in Figure 3.

Table 27 Cycle 1 Day 1: Geometric Mean Plasma PK parameters of Larotrectinib following a single oral administration of larotrectinib in paediatric patients with primary central nervous system tumours by age group and overall – Phase 2

PK Parameters[a]	Units	Cohort 3 (Primary Central Nervous System Tumors)					
		1 to 3 months N=1	1 to 2 years N=3	2 to 6 years N=10	6 to 12 years N=14	12 to 18 years N=1	All N=29
AUC_{0-4}	h*ng/mL	2420 (NC);1	715 (115.3);3	933 (201.3);9	1140 (61.4);14	875 (NC);1	1030 (105.5);28
AUC_{0-12}	h*ng/mL	NC	NC	614 (NC);1	NC	992 (NC);1	780 (34.9);2
AUC_{last}	h*ng/mL	2430 (NC);1	716 (115.3);3	842 (206.5);10	1170 (62.1);14	992 (NC);1	1010 (111.6);29
C_{max}	ng/mL	727 (NC);1	484 (105.4);3	614 (190.0);10	630 (72.9);14	728 (NC);1	614 (105.7);29
T_{max}[b]	h	0.98 (0.98, 0.98);1	1.00 (0.98, 1.00);3	0.99 (0.50, 1.03);10	1.00 (0.53, 1.02);14	0.42 (0.42, 0.42);1	1.00 (0.42, 1.03);29
T_{last}[b]	h	4.02 (4.02, 4.02);1	4.00 (3.95, 4.03);3	4.02 (1.00, 11.03);10	4.00 (3.85, 8.00);14	12.00 (12.00, 12.00);1	4.00 (1.00, 12.00);29
AUC_{0-4}/Dose	h*ng/mL/mg	86.3 (NC);1	21.7 (68.9);3	13.2 (194.4);9	12.0 (64.3);14	8.75 (NC);1	14.0 (113.2);28
AUC_{0-12}/Dose	h*ng/mL/mg	NC	NC	12.3 (NC);1	NC	9.92 (NC);1	11.0 (15.2);2
AUC_{last}/Dose	h*ng/mL/mg	86.7 (NC);1	21.7 (68.8);3	12.0 (200.7);10	12.3 (65.1);14	9.92 (NC);1	13.7 (117.9);29
C_{max}/Dose	ng/mL/mg	26.0 (NC);1	14.7 (62.0);3	8.73 (186.2);10	6.61 (74.9);14	7.28 (NC);1	8.31 (112.7);29

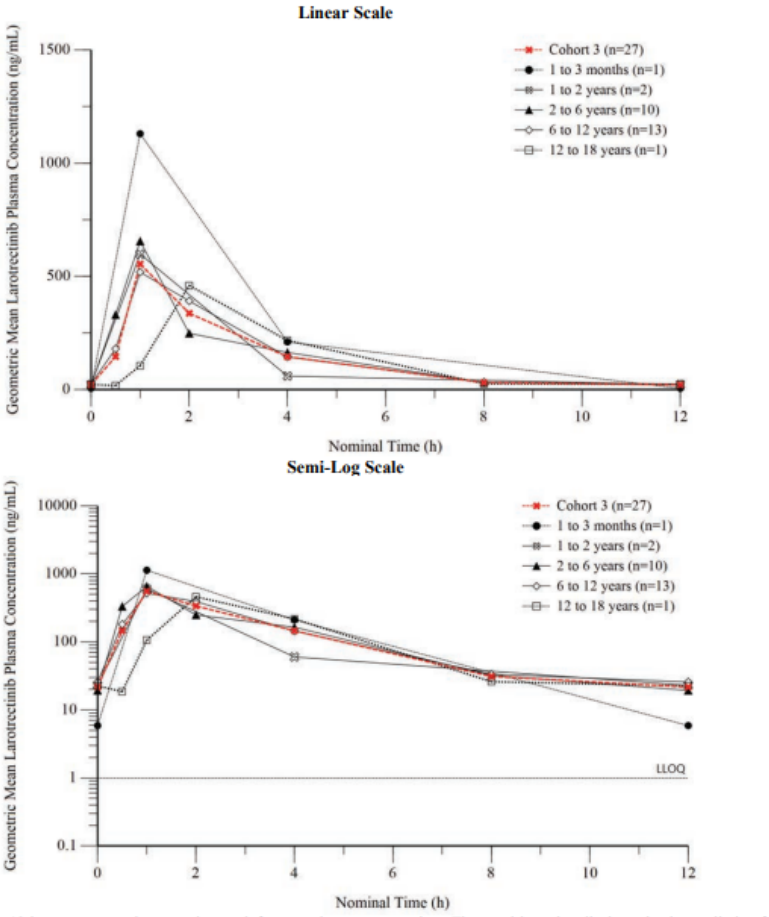
[a] Geometric Mean (Geometric CV%);N
[b] Median (Min; Max);N
NC = Not calculated
All patients were neurotrophic tyrosine kinase (NTRK) positive.

Table 28 Cycle 4 Day 1: Geometric Mean Plasma PK parameters of larotrectinib following a single oral administration of larotrectinib in paediatric patients with primary central nervous system tumours by age group and overall – Phase 2

PK Parameters[a]	Units	Cohort 3 (Primary Central Nervous System)					
		1 to 3 months N=1	1 to 2 years N=2	2 to 6 years N=10	6 to 12 years N=13	12 to 18 years N=1	All N=27
AUC_{0-4}	h*ng/mL	2220 (NC);1	1050 (1126.6);2	1410 (63.2);10	1430 (43.8);13	948 (NC);1	1390 (70.6);27
AUC_{0-12}*	h*ng/mL	2690 (NC);1	1390 (1611.1);2	1960 (53.1);10	2160 (43.1);13	1390 (NC);1	2000 (70.2);27
AUC_{last}	h*ng/mL	2230 (NC);1	1060 (1154.3);2	1380 (74.8);10	1480 (45.5);13	1290 (NC);1	1420 (74.9);27
C_{max}	ng/mL	1130 (NC);1	598 (590.4);2	695 (79.1);10	759 (52.2);13	460 (NC);1	719 (74.0);27
T_{max}[b]	h	1.00 (1.00, 1.00);1	1.02 (0.97, 1.08);2	1.01 (0.85, 3.97);10	1.00 (0.00, 3.95);13	2.20 (2.20, 2.20);1	1.00 (0.00, 3.97);27
T_{last}[b]	h	4.03 (4.03, 4.03);1	4.07 (4.00, 4.13);2	4.00 (2.00, 7.93);10	4.00 (3.75, 8.03);13	7.83 (7.83, 7.83);1	4.00 (2.00, 8.03);27
CL_{ss}/F*	L/h	13.4 (NC);1	22.8 (420.2);2	36.8 (52.7);10	45.2 (46.6);13	71.7 (NC);1	38.7 (68.1);27
AR AUC_{0-4}	.	0.920 (NC);1	1.40 (112.8);2	1.58 (232);9	1.24 (72.6);13	1.08 (NC);1	1.34 (115.7);26
AUC_{0-4}/Dose	h*ng/mL/mg	61.7 (NC);1	33.1 (319.6);2	19.6 (64.8);10	14.6 (48.5);13	9.48 (NC);1	18.0 (74.2);27
AUC_{0-12}/Dose	h*ng/mL/mg	74.6 (NC);1	43.9 (420.2);2	27.2 (52.7);10	22.1 (46.6);13	13.9 (NC);1	25.8 (68.1);27
AUC_{last}/Dose	h*ng/mL/mg	61.9 (NC);1	33.4 (325.6);2	19.2 (72.2);10	15.2 (49.8);13	12.9 (NC);1	18.4 (75.3);27
C_{max}/Dose	ng/mL/mg	31.4 (NC);1	18.9 (192.4);2	9.65 (84.5);10	7.80 (56.7);13	4.60 (NC);1	9.30 (81.1);27

* = The 12-hour concentration was imputed from predose concentration for the calculation of AUC_{0-12} and CL_{ss}/F
[a] Geometric Mean (Geometric CV%);N
[b] Median (Min; Max);N
AR = Accumulation ratio
NC = Not calculated
All patients were neurotrophic tyrosine kinase (NTRK) positive.

Figure 3 Geometric Mean Plasma Concentrations of larotrectinib following multiple oral administrations of larotrectinib BID in paediatric patients with primary central nervous system by age group and overall – Phase 2 Cohort 3 – Cycle 4 Day 1 (Linear and Semi-Lo g Scales)



Notes: The 12-hour concentration was imputed from predose concentration. The semi-log plot displays the lower limit of quantification (LLOQ) of 1.00 ng/mL. Phase 2 Cohort 3 patients were neurotrophic tyrosine kinase (NTRK) positive. Samples collected were at 1 and 4 hours post-dose, except for a few older patients (2-6 years [n=2], 6-12 years [n=2], 12-18 years [n=1]) where additional samples were also collected at 0.5 [n=5], 2 [n=5]and 8 [n=4] hours post-dose.

2.3.4. Update of the integrated Larotrectinib popPK analysis

Data

Study data from 7 clinical studies (using all available PK data from studies (LOXO internal study number/Bayer internal study number) LOXO-TRK-16007/20291, LOXO- TRK-16012/20295, LOXO-TRK-14001/20288, and 20381 and LOXO-TRK- 16009/20292, and new data for studies LOXO-TRK-15002/20289, LOXO-TRK- 15003/20290 with a data cut of 23 September 2024) were included in this population PK analysis. These included data from four Phase I studies in healthy subjects (Studies LOXO-TRK-16007/20291, LOXO-TRK-16009/20292, LOXO-TRK-16012/20295, and 20381) and three Phase I, I/II, and II studies in cancer patients (Studies LOXO-TRK- 14001/20288, LOXO-TRK-15002/20289, LOXO-TRK-15003/20290). Plasma larotrectinib concentration data, dosing information, demographic variables, and laboratory values were used in the analysis. These data were analysed using a nonlinear mixed-effects modelling approach that included development of a base model, covariate search, and model refinement. Analysis was performed with NONMEM. The first order conditional estimation method of NONMEM with interaction (FOCE INTER) was used for PK model development. R was used for simulations for the final dosing regimens. A summary of paediatric patient data is presented in Table 29.

Table 29. Summary of paediatric patient demographics

	NTRK Fusion N=146	Non-*NTRK* Fusion N=8	Total N=154
Age (years)			
Median	4.96	14.13	5.13
Range	0.1, 20.5	3.0, 17.6	0.1, 20.5
Age category, n (%)			
<3 months	13 (9)	0	13 (8)
3 months to <1 year	23 (16)	0	23 (15)
1 to <2 years	11 (8)	0	11 (7)
2 to <6 years	34 (23)	2 (25)	36 (23)
6 to <12 years	37 (25)	1 (13)	38 (25)
12 to <16 years	16 (11)	3 (38)	19 (12)
≥16 years	12 (8)	2 (25)	14 (9)
Gender, n (%)			
Female	67 (46)	4 (50)	71 (46)
Male	79 (54)	4 (50)	83 (54)
Race, n (%)			
White	89 (61)	2 (25)	91 (59)
Asian	28 (19)	1 (13)	29 (19)
Other	17 (12)	4 (50)	21 (14)
Black or African American	2 (1)	1 (13)	3 (2)
Native Hawaiian or Other Pacific Islander	1 (<1)	0	1 (<1)
Multiple	1 (<1)	0	1 (<1)
Patient declined to state	8 (5)	0	8 (5)
Ethnicity, n (%)			
Non-Hispanic or Latino	124 (85)	4 (50)	128 (83)
Hispanic or Latino	12 (8)	3 (38)	15 (10)
Declined to state	10 (7)	1 (13)	11 (7)
Body weight (kg)			
Median	18.05	44.28	19.00
Range	3.2, 89.2	14.7, 82.7	3.2, 89.2
BSA (m^2)			
Median	0.73	1.34	0.76
Range	0.2, 2.1	0.6, 2.0	0.2, 2.1

Abbreviations: BSA = body surface area; N = total number of patients (100%); n = number of patients in category/with event; *NTRK* = neurotrophic tyrosine receptor kinase

Notes: Due to rounding, percentages may sometimes not add up to 100 (e.g., for age categories).
Percentages are based on the number of patients (N) specified in the column header.
Baseline values are those measured closest to but not after the first dose of larotrectinib.

Observed concentrations

While Study 20290 is an open-label, Phase 1/2 study in paediatric patients aged from birth through 21 years, Study 20289 is a Phase 2, open-label "basket" study in patients 12 years of age or older. The larotrectinib concentrations from these two studies are compared to evaluate the exposure in paediatrics compared to that in adults. The common sampling timepoints in both studies: PK samples were obtained at 0 hr (predose), 1 hr, and 4 hr postdose at steady state in both studies are listed in Table 30 by different age groups for patients receiving the recommended dose (100 mg/m2 up to 100 mg BID) from both studies for direct comparison. The data here provided direct comparison on actual larotrectinib concentrations observed with all available data from patients across different age groups in Phase 2 Studies 20289 and 20290. The 1 hr concentration after multiple doses represents the steady state Cmax value comparison across different age groups. The median larotrectinib concentration value for the youngest patient population is higher than that for the older age groups; however, the range of the concentration is mostly overlapping with the range in the other age groups with only one outlier high value. The concentration at later timepoint at steady state (4 hr concentration after multiple doses) is shown in Figure 4 compared to the range for the adults.

Table 30. Summary statistics for concentrations of Larotrectinib in PLASMA (PK analysis set – all patients with 100 mg or 100 mg/m2 BID) by age

					Larotrectinib Concentration (ng/mL)								
Age group	Analysis Visit [a]	Time point	n	n ≥ LLOQ	Geom. Mean	Geom. SD	Geom. CV(%)	Arithm. Mean	Arithm. SD	Arithm. CV(%)	Min	Median	Max
<3 month	Cycle 1 Day 1	1H	11	11	1910	1.65	53.10	2130	1070	50.17	727	1700	4700
		4H	11	11	1120	1.61	50.30	1250	676	53.95	639	1010	2880
	Cycle 4 Day 1	0H	10	10	15.8	1.93	73.54	18.6	9.52	51.16	5.63	20.3	29.8
		1H	10	10	1160	1.68	55.90	1340	912	68.23	585	1180	3770
		4H	8	8	328	2.11	86.17	404	261	64.66	79.0	352	921
3 to <6 months	Cycle 1 Day 1	1H	4	4	1160	2.23	95.03	1470	1080	73.80	512	1260	2840
		4H	4	4	110	2.83	139.43	170	195	114.57	38.7	91.0	460
	Cycle 4 Day 1	0H	4	4	38.6	6.50	567.84	145	250	172.29	6.55	27.1	520
		1H	4	4	781	3.26	174.30	1240	1180	95.17	253	998	2720
		4H	4	4	113	2.01	79.43	132	72.5	54.78	43.5	141	204
6 to <12 months	Cycle 1 Day 1	1H	17	17	1080	2.48	113.02	1580	1430	90.49	292	957	5340
		4H	17	17	196	3.67	210.67	384	448	116.65	16.6	230	1520
	Cycle 4 Day 1	0H	17	17	16.1	4.10	251.40	101	350	347.99	1.72	13.6	1460
		1H	17	17	797	1.94	74.57	987	694	70.37	366	920	2850
		4H	17	17	121	2.37	105.16	170	152	89.60	25.2	131	621
1 to <2 years	Cycle 1 Day 1	1H	9	9	655	1.83	66.11	755	391	51.84	208	768	1470
		4H	9	9	63.2	4.32	273.88	214	456	213.00	9.71	38.1	1420
	Cycle 4 Day 1	0H	7	6	6.26	5.40	402.44	23.0	46.4	201.75	<LLOQ	5.81	128
		1H	7	7	409	2.40	107.60	614	747	121.68	157	393	2280
		4H	7	7	80.4	4.86	334.33	173	192	111.42	6.40	136	563
2 to <6 years	Cycle 1 Day 1	1H	32	32	631	2.30	99.79	827	648	78.36	39.6	713	3420
		4H	31	31	69.4	2.46	111.41	93.0	68.1	73.22	2.66	75.7	305
	Cycle 4 Day 1	0H	30	30	17.6	2.16	90.29	25.8	36.1	139.64	4.38	15.6	204
		1H	28	28	779	1.82	65.95	900	462	51.33	108	778	2190
		4H	29	29	136	2.09	84.87	174	126	72.75	30.2	164	575
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
6 to <12 years	Cycle 1 Day 1	1H	36	36	525	2.83	139.36	819	853	104.14	42.4	635	3980
		4H	36	36	157	2.42	108.61	243	282	116.28	39.0	143	1110
	Cycle 4 Day 1	0H	31	31	21.7	2.50	114.59	56.5	190	336.87	7.78	22.3	1080
		1H	32	32	547	3.00	152.69	791	541	68.38	16.1	736	2360
		4H	32	32	155	1.95	74.68	188	110	58.61	35.9	169	415
12 to <18 years	Cycle 1 Day 1	1H	29	29	489	2.17	90.48	610	360	59.02	66.5	556	1740
		4H	28	28	125	2.11	86.04	165	151	91.30	33.9	116	789
	Cycle 4 Day 1	0H	22	19	8.32	3.54	198.96	13.2	10.0	75.78	<LLOQ	11.1	37.1
		1H	23	23	435	2.43	109.69	568	348	61.37	27.0	515	1410
		4H	22	22	117	1.79	63.88	135	67.2	49.71	31.7	125	254
≥18 years	Cycle 1 Day 1	1H	214	214	443	2.95	149.26	644	504	78.17	1.48	557	3360
		4H	214	213	164	2.68	128.26	251	267	106.53	<LLOQ	161	2260
	Cycle 4 Day 1	0H	172	158	11.2	4.19	260.13	30.3	73.3	241.86	<LLOQ	11.2	739
		1H	172	171	374	2.61	122.56	492	311	63.29	<LLOQ	454	2200
		4H	169	169	133	2.13	87.71	179	174	97.38	6.32	139	1480
All Ages in the Study	Cycle 1 Day 1	1H	352	352	523	2.84	140.80	780	721	92.48	1.48	597	5340
		4H	350	349	154	2.91	145.60	265	341	128.56	<LLOQ	147	2880
	Cycle 4 Day 1	0H	293	275	12.7	3.79	221.54	36.4	122	335.89	<LLOQ	13.2	1460
		1H	293	292	466	2.62	123.50	640	496	77.39	<LLOQ	515	3770
		4H	288	288	135	2.18	91.24	181	162	89.70	6.32	145	1480

Abbreviations: Arithm. = arithmetic; BID = twice daily; CV = coefficient of variation; Geom. = geometric; Max = maximum; Min = minimum; LLOQ = lower limit of quantification; n = number of patients with evaluation category; NC = not calculated; SD = standard deviation

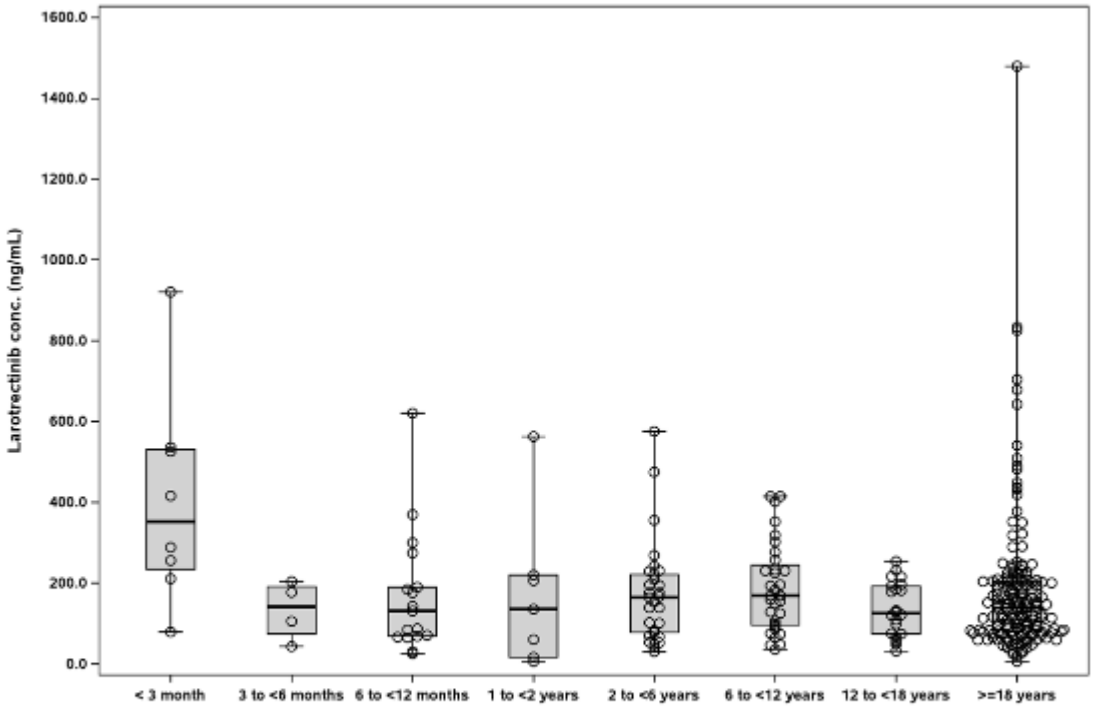
Notes: LLOQ values are 1 5 20.

No missing values.

Summary statistics are calculated only for data ≥3, except from min and max.

a For Study 20289, values available from Cycle 3 or Cycle 5 were used instead of Cycle 4.

Figure 4. Box plot of Larotrectinib Concentration at 4 hours at steady-state (PK analysis set – all patients with 100 mg or 100 mg/m2 BID) by age



Abbreviations: BID = twice daily
Box: 25th and 75th percentile; horizontal line: median; vertical lines extend from the box as far as the data extends, including outliers.
For Study 20289, concentration data available from Cycle 3 or Cycle 5 were used. For Study 20290, concentration data from Cycle 4 were used.

Methods

The analysis included an update of the previously developed population PK model using all available PK data through 23 September 2024 from the studies listed in Section 4.1. The new analysis included a validation of the previously developed model on the updated pooled dataset and a development of an updated final model after qualification and refinement (emphasis on paediatric patients and race/ethnicity/region effects).

The pre-defined covariates evaluated in this analysis are listed in Table 31. Detailed descriptions of the covariates, including derivation methods, are provided in Table 32.

Table 31. Covariates evaluated in the Population PK Model

Covariate	PK Parameter Groups		
	Volume	Clearance	Absorption/Bioavailability
Age[a]	X	X	
Age category[a]	X	X	
Albumin	X	X	
BSA[b]	X	X	
Body weight[b]	X	X	
Creatinine clearance[c]		X	
Dose	X	X	X
Formulation			X
Ethnicity	X	X	
Liver function tests[d]		X	X
Patient status	X	X	X
Race	X	X	
Serum creatinine[c]		X	
Sex	X	X	X
Food			X
Geographic region	X	X	

[a] Age and age category were both explored; however, only a single covariate was included in the final covariate model.
[b] Body weight and BSA were both explored; however, only a single body size measure was included in the final covariate model.
[c] Creatinine clearance and serum creatinine were both explored; however, only a single renal function measure was included in the final covariate model.
[d] Liver function tests included ALP, ALT, AST, and TB.
ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate aminotransferase; BSA=body surface area; PK=pharmacokinetic; TB=total bilirubin.

Table 32. Description of Covariates and Associated Deviation Methods

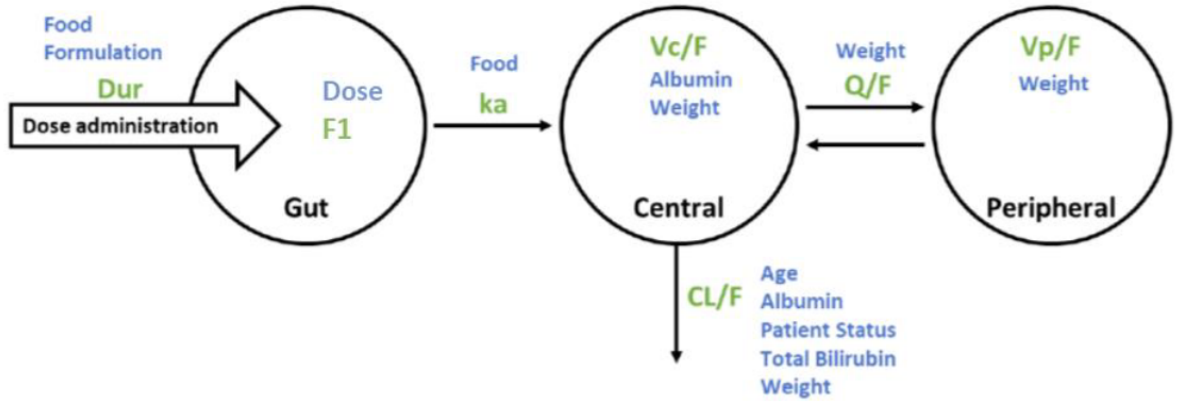
Covariate (Abbreviation)	Description and/or Derivation
Age category (AGEC)	1 to <3 months, 3 to <6 months, 6 to <12 months, 1 to <2 years, 2 to <6 years, 6 to <12 years, ≥12 years
Body surface area (BSA)	$BSA\ (m^2) = \sqrt{\frac{Height\ (cm) \times Weight(kg)}{3600}}$
Creatinine clearance (CLCR)	$CLCR = \frac{(140 - age) \times Body\ weight\ (kg)}{serum\ creatinine\ (mg/dL) \times 72} \times 0.85(if\ female)$
Dose (DOSE)	Dose per administration (e.g., 50 mg QD=50 and 50 mg BID=50)
Patient status (PATS)	0=healthy volunteer, 1=patient
Sex (SEX)	0=female, 1=male

BID=twice daily; BSA=body surface area; QD=once daily.

Previously Developed Population PK Model

The previously developed population PK model for larotrectinib following oral administration was a 2-compartment disposition model with sequential zero-order and first-order absorption Figure 5.

Figure 5. Diagram of Previously Developed Population PK Model for Larotrectinib



CL/F=apparent clearance; Dur=duration of zero-order absorption; F1 = relative bioavailability; ka=first-order absorption rate constant; PK=pharmacokinetic; Q/F=apparent inter-compartmental clearance; Vc/F=apparent central volume of distribution; Vp/F=apparent peripheral volume of distribution.
Note: Green words represent structural PK parameters. Black words represent structural components of the PK model. Blue words represent covariates associated with the nearby structural PK parameters.

Between-subject variability terms were included on apparent clearance (CL/F), apparent central volume of distribution (Vc/F), first-order absorption rate constant (ka), and duration of zero-order absorption (Dur). The residual error model included a proportional error term. The extrinsic factors of food (fed versus fasted) and formulation (capsule versus solution), as well as the intrinsic factors albumin, total bilirubin, age, body weight, and patient status (healthy versus patient) were all found to influence the PK of larotrectinib. Moreover, a dose effect was added on F1.

Larotrectinib PK in the paediatric population (i.e., age < 18 years) was well characterized by accounting for body size related differences using standard allometric scaling (0.75 for clearance parameters and 1.0 for volume parameters) and by capturing CL/F maturation using a sigmoidal function based on postnatal age (in years) with a fixed hill coefficient of 1 (Equation below).

$$CL_i = \theta_{CL} * \left(\frac{PNA^{\gamma}}{PNA^{\gamma} + Age_{50}^{\gamma}} \right)$$

Age_{50}=post-natal age at which 50% of adult clearance is achieved in years; CL_i=individual clearance; γ=Hill coefficient; PNA=post-natal age in years; θ_{CL}=typical adult clearance

Evaluation of popPK model updates

The population PK analysis used the previously developed population PK model for larotrectinib as starting point. The population PK analysis was integrated with the new data covering the same questions and covariates as the already available population PK approach. Exploratory analyses and graphical evaluations using standard diagnostic plots were conducted to decide whether the analyses needed to be updated.

Simulations

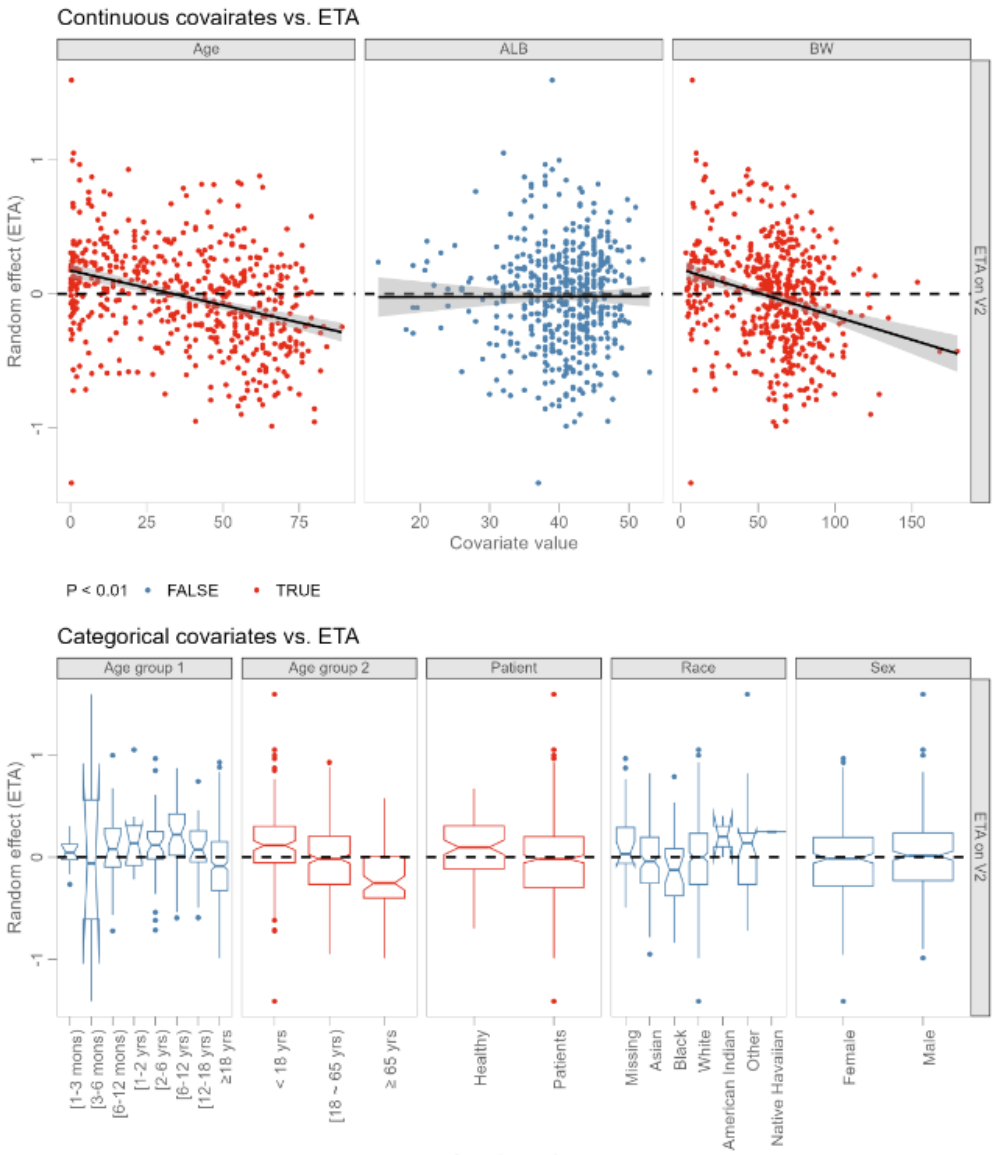
Individual paediatric (<18 years of age) simulation subjects (N=1000 per age group) were generated by sampling from distributions of the covariates in the analysis dataset or by utilizing literature sources, if deemed necessary. Individual adult simulation subjects were generated by re-sampling with replacement from the adult subjects in the population PK dataset. A collection of typical parameter estimates (N=100) was randomly selected from the uncertainty distribution of those parameters. For each simulation replicate, one set of typical parameter estimates was used, and individual PK parameters were generated for each simulation subject using the covariates for that subject and the between-subject variability distributions for the PK parameters from the final model. A total of 100 simulation replicates were prepared, one for each set of typical parameter estimates. For each simulation replicate, the individual simulation subject PK parameters were used to generate concentration-time profiles from which Cmax and AUC0-24 were calculated on Day 1 and at steady-state. Simulation results were summarized by replicate first, and then those summary statistics were summarized for presentation.

Results

The previously developed population PK model for larotrectinib following oral administration was used to perform a model validation on the extended dataset before applying any data exclusions. The previously developed population PK model for larotrectinib was used to perform a prediction corrected VPC (N= 1000) using the updated dataset. It showed that the previously developed model captures the data well, with the median and 95th observed percentiles of the data being mostly captured within the 95% CI of the simulated data. Nonetheless, we observe that the model tends to overpredict the variability in the data, especially for the lower concentrations where the observed 5th percentile tends to be higher than the simulated 5th percentile and its associated 95% CI.

The pcVPC for the validation of the previous model with the updated dataset when stratified by age groups confirmed that the maturation function previously identified allows to capture well larotrectinib PK across all age groups with the median of the data remaining within the simulated 95% CI of the median. The exploration of the relationships between ETA distributions and both continuous and categorical covariates showed that residual trends were visible between the ETA on Vc/F and age, body weight and patient status (Figure 6). For this reason, a refinement of the previously developed PK model was conducted with focus on further exploring the impact of these covariates on larotrectinib Vc/F.

Figure 6. Categorical and Continuous Covariate Eta Plots for Vc/F from the Previous Population PK Model for Larotrectinib



First, considering the known correlation between baseline age and body weight and that the effect of body weight on volume of distribution was already accounted for by standard allometric scaling, an age effect was introduced on Vc/F in adults only using a power relationship similarly to the effect already included on CL/F. This led to a highly significant drop in OFV (delta of -99 points) and allowed addressing the trends visible for both age and body weight (Figure 11). The refined model still showed residual trends between healthy subjects and patients on Vc/F; the inclusion of an effect of patient status on Vc/F led to a further drop in OFV of 8.3 points and allowed addressing residual differences between the two sub-groups (Figure 11) while maintaining model stability and a low condition number (32.1). Finally, the refined model was updated using time- varying body weight as compared to baseline body weight which allowed improving further the description of individual data particularly in the youngest age groups (delta of -71.8 points in the OFV).

The final PK model for larotrectinib (Table 33) has a 2-compartment disposition with sequential zero-order and first-order absorption model of larotrectinib following oral administration. The updated covariate model for larotrectinib included effects of albumin on both CL/F and Vc/F, food status on ka,

total bilirubin on CL/F, weight as fixed allometry on clearance and volume related parameters (i.e., CL/F, Vc/F, Q/F, Vp/F), the effects of food and formulation on Dur, and the effect of dose on F1 as described in the previous model. In addition, effects of age and patient status were included as described above on CL/F and Vc/F. An additive term was included in the error model and fixed to a very small value (i.e., 0.001) to improve model stability. As compared to the previously developed model, age and patient status effects were extended to Vc/F. No other covariates were found to be statistically significant or clinically relevant. In Figure 7 the selected Goodness-of-Fit Plots for the final Population PK Model for Larotrectinib are presented, and Figure 8 shows the prediction-Corrected VPC for the Final Population PK Model for Larotrectinib stratified by age group. The simulated Larotrectinib exposure (Figure 9) grouped by age and body weight shows a comparison of the expected exposure in children to the exposure in adult patients given 100 mg BID (grey shaded area).

Table 33. Parameter Estimates and Bootstrap results for the Final Population PK Model for Larotrectinib

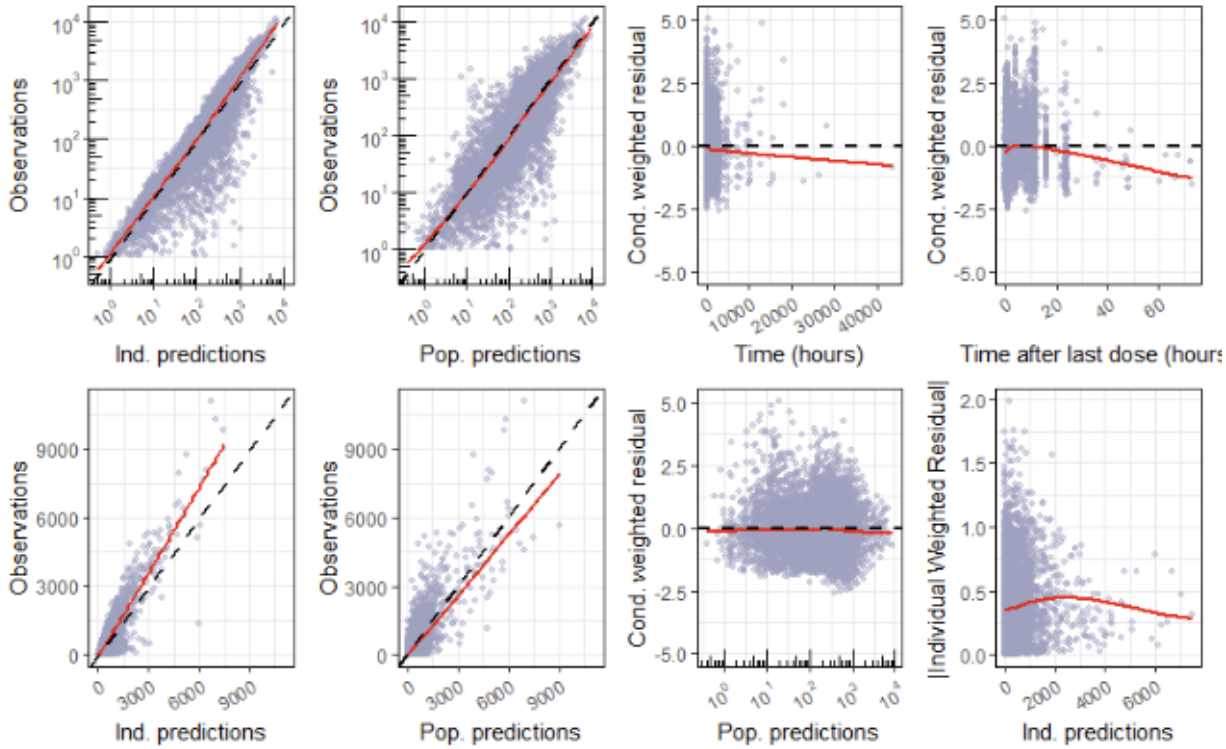
Parameter	Estimate	RSE%	Bootstrap Median	Bootstrap 95%CI	Shrinkage
Typical Values					
1. Ka (1/h)	4.66	16.7	4.57	3.58 – 5.93	
2. CL/F (L/h)	85.7	4.15	85.6	77.5 – 94.6	
3. Vc/F (L)	204	4.72	203	179 – 229	
4. Vp/F (L)	206	39.7	200	96.5 – 351	
5. Q/F (L/h)	5.92	7.07	5.91	5.10 – 6.83	
6. Dur (h)	0.600	2.45	0.591	0.516 – 0.656	
7. Feed effect on Dur	2.28	22.1	2.46	1.46 – 3.54	
8. Form effect on Dur	-0.679	8.98	-0.666	-0.793 – -0.543	

Parameter		Estimate	RSE%	Bootstrap Median	Bootstrap 95%CI	Shrinkage
9.	Weight on CL/F (allometry)	0.750 Fixed	n/a	0.750	n/a	
10.	Age effect on CL/F (Age >18 years)	-0.424	10.8	-0.424	-0.526 – -0.329	
11.	Maturation function TM50 estimate	0.369	24.0	0.368	0.213 – 0.626	
12.	Weight on Vc/F (allometry)	1.00 Fixed	n/a	1.00	n/a	
13.	Albumin effect on CL/F	0.819	19.1	0.835	0.495 – 1.10	
14.	Feed effect on Ka	-0.877	5.26	-0.866	-0.933 – -0.715	
15.	Albumin effect on Vc/F	0.681	18.4	0.687	0.407 – 1.05	
16.	Total bilirubin effect on CL/F	-0.204	22.5	-0.202	-0.282 – -0.120	
17.	Patient effect on CL/F	0.275	36.1	0.272	0.110 – 0.469	
18.	Dose (200/400) effect on F1	0.364	43.6	0.345	0.0917 – 0.685	
19.	Dose (600/700) effect on F1	0.936	23.0	0.906	0.562 – 1.40	
20.	Age effect on Vc/F (Age >18 years)	-0.395	12.0	-0.395	-0.484 – -0.287	
21.	Patient effect on Vc/F	0.239	36.0	0.227	0.0775 – 0.405	
Between Subject Variability						
1.	On Ka	1.08	17.0	1.06	0.758 – 1.46	36.2%
2.	On CL/F	0.225	9.11	0.219	0.183 – 0.263	4.40%

Parameter		Estimate	RSE%	Bootstrap Median	Bootstrap 95%CI	Shrinkage
3.	On Vc/F	0.159	14.0	0.150	0.105 – 0.191	20.5%
6.	On Dur	0.303	9.17	0.294	0.134 – 0.460	52.5%
Residual Error						
1.	Proportional residual error	0.272	3.82	0.271	0.251 – 0.292	6.20%
2.	Additive residual error	0.00100 Fixed	n/a	0.00100	0.00100 – 0.00100	6.20%

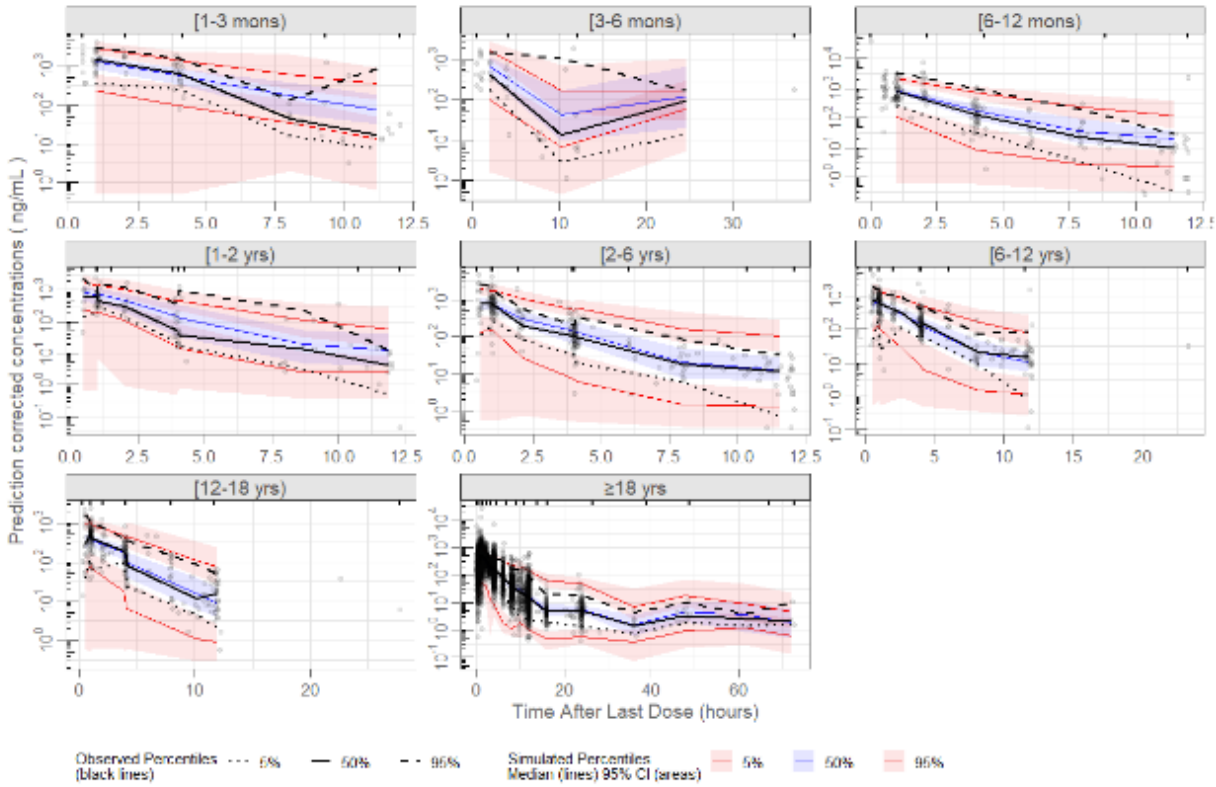
Source: baye-param-gof-vpc-ppk-laro-2024-v5.Rmd; run037-baye-param-gof-vpc-cov-ppk-Larotrectinib-v6.html
CL/F=apparent clearance; Dur=duration of zero-order absorption; ka=first-order absorption rate constant; PK=pharmacokinetic; Q/F=apparent inter-compartmental clearance; RSE=relative standard error of the estimate; Vc/F=apparent central volume of distribution; Vp/F=apparent peripheral volume of distribution, CI=confidence intervals.

Figure 7. Selected Goodness-of-Fit Plots for Final Population PK Model for Larotrectinib



Source: baye-param-gof-vpc-ppk-laro-2024-v5.Rmd; run037-baye-param-gof-vpc-cov-ppk-Larotrectinib-v6.html
Cond=conditional; Ind=individual; PK=pharmacokinetic; Pop=population.
Note: The circles represent individual data points, the red lines represent loess smooth curves, and the dashed black lines represent either the line of unity (y=x) or the x-axis (y=0).

Figure 8. Prediction-Corrected VPC for the Final Population PK Model for Larotrectinib Stratified by Age Group



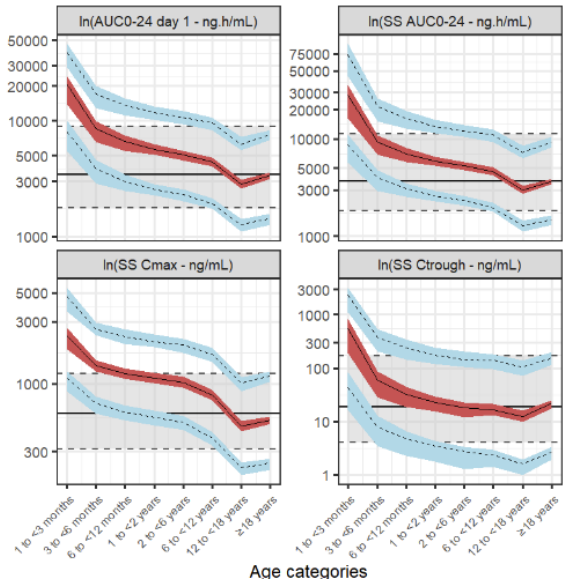
Source: baye-param-gof-vpc-ppk-laro-2024-v5.Rmd; run037-baye-param-gof-vpc-cov-ppk-Larotrectinib-v6.html

PK=pharmacokinetic; VPC=visual predictive check.

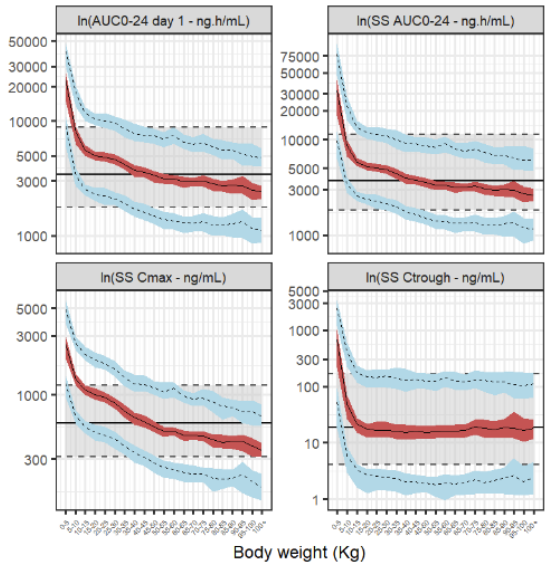
Note: The black dots represent prediction-corrected observed data, the black solid line represents the median of the prediction-corrected observed data, and the black dotted and dashed lines represent the 5th and 95th percentiles of the prediction-corrected observed data respectively. The blue solid line represents the median of the prediction-corrected simulation data, the red solid lines represent the 5th and 95th percentiles of the prediction-corrected simulation data, the red shaded areas represent the 95% confidence interval for the 5th and 95th percentiles of the predicted data, the blue shaded areas represent the 95% confidence interval for the median of the predicted data.

Figure 9. Simulated Larotrectinib Exposure Grouped by Age (A) and Body Weight (B)

A



B



Source: baye-laro-sim-20241216-v1.Rmd
$AUC_{0\text{-}24}$=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% confidence interval for the 5th and 95th percentiles of the simulated data (90% prediction interval). The black dashed line within the blue shaded region represents the 5th and 95th percentiles of the simulated data. Red shaded region represents the 95% confidence interval for the 50th percentile (median) of the simulated data. The solid black line within the red shaded region represents the 50th percentile (median) of the simulated data. Grey shaded region represents the 5th to 95th percentiles of the adult exposure for the patients in the population PK dataset. The horizontal dashed lines represent the 5th and 95th percentiles and the horizontal solid line represents the 50th percentile (median) of the adult exposure for the patients in the population PK dataset.

2.3.5. Discussion on clinical aspects

In this variation, the MAH submitted a final report for Larotrectinib PIP03 report PH-003410 for the larotrectinib paediatric clinical study 20290.

The PIP03 report evaluated the treatment of paediatric patients with primary CNS tumours harbouring an NTRK gene fusion. The PIP03 population was a subset of patients from study 20290 (SCOUT).

Study 20290 is an ongoing global, multicentre, open-label, phase 1/2 study in paediatric patients aged from birth to 21 years with advanced solid or primary CNS tumours.

As of DCO (20 Jul 2023), 154 patients were included in study 20290 and constituted the FAS. All patients in the phase 2 part received larotrectinib 100 mg/m^2 BID.

An interim analysis as of DCO revealed an ORR (primary endpoint) of 68% (95% CI 60, 76), regardless of presence of NTRK gene fusion. Median DOR was 36.9 months.

In total 152/154 (98.7%) patients experienced a TEAE, of which 102 (66.2%) were grade ≥3 and 69 (44.8%) SAEs. Study treatment discontinuation due to TEAEs was reported for 13 (8.4%) patients.

Among patients in study 20290, 58/154 (37.7%) experienced neurological TEAEs of any grade and 12/154 (7.8%) grade ≥3. The most common neurologic grade ≥3 TEAEs were ataxia (3.2%), cognitive

disturbance (2.6%), neuralgia, paraesthesia, and `other´(e.g., dysarthria, dysphagia, and pyramidal tract symptoms) (1.3% each).

Study PIP03

The PIP03 population comprised a total of 40 paediatric patients from birth to less than 18 years of age with primary CNS tumours harbouring NTRK gene fusions. The PIP03 patients were included in both the phase 1 and phase 2 parts of study 20290. Of the PIP03 patients, 22 had high-grade gliomas (HGG), 13 had low-grade gliomas (LGG), and five had non-gliomas.

DCO for the PI03 analyses was 18 May 2024.

Primary endpoint in the PIP03 phase 2 study part was ORR by RANO criteria. Secondary endpoints included BOR according to RANO criteria, DOR, PFS, and OS. Secondary endpoint palatability was analysed in a separate study analysis set of 17 patients who received the new 2% oral larotrectinib solution.

Pharmacokinetics PIP03

The objective of the sixth interim PK analysis of study 20290 (LOXO-TRK-15003) was to assess the plasma larotrectinib PK of orally administered larotrectinib in 40 paediatric patients: 11 patients with primary CNS tumours (dose expansion cohort) from the phase 1 portion and 29 patients with primary CNS tumours (cohort 3) from the phase 2 portion of the study. The doses given in phase 1 dose expansion cohort were 98.7 to 112 mg/m^2 in the 2-6 years paediatric age group and 64.5 to 104 mg/m^2 in other paediatric age groups. For this reason, the plasma concentration results cannot be compared to the phase 2 results, and adults.

The recommended phase 2 dose was in accordance with the approved SmPC, i.e., 100 mg/m^2 BID, not to exceed a dose of 100 mg BID. The larotrectinib geometric mean AUC0-4 and Cmax observed for the 1-2 years, 2-6 years, and 6-12 years age groups on day 1 ranged from 715 to 1140 h*ng/mL and 484 to 728 ng/mL, respectively. The AUC0-4 and Cmax for the children <3 months of age was 2420 h*ng/mL and 727 ng/mL, respectively. The larotrectinib geometric mean AUC0-4 and Cmax observed for the 1-2 years, 2-6 years, and 6-12 years age groups on day 112 ranged from 948 to 1430 h*ng/mL and 460 to 759 ng/mL. The AUC0-4 and Cmax for the children <3 months of age was 2220 h*ng/mL and 1130 ng/mL, respectively.

These results, that the exposure is approximately 2-2.5 times higher in children <3 months of age compared to older children is in line with results previously reported for AUC0-24.

Updated paediatric PK analysis

The applicant presented, as requested, a comparison of all observed PK concentrations in children (18 days old to 21 years old) across age groups (from study 20290/LOXO-TRK-15003) and compared to exposure in adults. In addition, the applicant provided an updated population PK analysis for larotrectinib with specific emphasis on evaluating if the updated data confirm the maturation function previously identified to describe larotrectinib PK in younger paediatric age group.

The analyses of observed concentrations and simulations from the updated population PK analyses shows that the exposure in children <3 months of age is significantly higher compared to both older children and adults. In order to avoid unnecessary overexposure, and potential risks for long-term side effects, the MAH is requested to re-evaluate the dose in the youngest age group, i.e., <3 months of age, with the aim to match the exposure (primarily AUC) to older children at steady state.

Efficacy PIP03

Efficacy analyses were performed in two analysis sets. The main efficacy analysis set (EAS) comprised patients who received at least one dose of larotrectinib and had measurable disease at baseline as assessed by the investigator and RANO or RECIST 1.1 criteria. The second EAS (EAS2) comprised patients who received at least one dose of larotrectinib and had measurable disease at baseline as assessed by IRC and RANO criteria. The two analysis sets comprised 34 (EAS) and 27 (EAS2) patients, respectively.

ORR in the EAS was 60% (95% CI 39, 79) and median DOR was not estimable (NE). Four patients had a BOR of CR. BORs of PR occurred in 11 (32%) patients in EAS.

Although all analyses in PIP03 were exploratory, pre-specified thresholds were defined in the agreed EMEA-001971-PIP03-18-M02 (11 Aug 2022) for ruling out efficacy in PIP03. These boundaries ($\leq$10% ORR in the HGG subset and $\leq$30% DCR in the LGG subset) were crossed with the obtained results 56% ORR (95% CI 30, 80) in the HGG subset and DCR 89% (95% CI 52, 100) in the LGG subset.

Overall, efficacy results were relatively comparable across the subgroups HGG, LGG, and non-glioma. Due to the limited number of patients in each subgroup, though, subgroup results have to be interpreted with caution.

Larotrectinib was effective across different NTRK gene fusions. A majority of the NTRK gene fusion isoforms (17/25 evaluable patients) were reported in 1 patient each.

At the time of the DCO, 18 patients (53%) in the EAS had progressed or died, and the remaining patients were censored. The median PFS for patients in the EAS was 19.8 months (95% CI 13.1, NE), with a median follow-up time of 25.1 months. Median OS was NE in the EAS. Overall, efficacy results were comparable between EAS and EAS2.

The PIP03 results showed that larotrectinib is efficacious in paediatric patients with primary CNS tumours with NTRK gene fusions. Data from the palatability analysis set, the pooled paediatric and adult population, and the comparison with historical external controls were hampered by limited sample sizes and limited data for key analyses (the latter applicable to the historical comparison) but were generally in line with the results of PIP03.

Safety PIP03

The PIP03 SAF comprised all 40 patients in the PIP03 population. At DCO, 16 (40%) of the SAF patients were still on study treatment, four (10%) were off treatment in the wait and see period, and 20 (50%) had discontinued study treatment. The most common reason for treatment discontinuation was disease progression (12 [30%] patients). One patient discontinued treatment due to death.

The median time on treatment was 20.8 months (range 1.2 to 65.2 months).

Overall, all SAF patients (100%) experienced $\geq$1 TEAE, with same incidences among patients with HGG, LGG, and non-glioma. Grade $\geq$3 TEAEs were reported in 63% of the patients and SAEs in 60% of the patients. A total of three patients (8%) had a fatal (grade 5) TEAE. Two of these were TEAEs disease progression and one was reported as a TEAE not otherwise specified.

The most common TEAEs by PT in the SAF were vomiting (45%), pyrexia (38%), and ALT increased, cough, and upper respiratory tract infection (35% each). The most common grade $\geq$3 TEAE was neutrophil count decreased (10%, 23% all grades). The most common SAE was headache (8%). There were no events of febrile neutropenia.

Due to the small sample size in the infants and toddlers and adolescent subgroups (n=4 each), a meaningful comparison of the TEAE profile between the age groups was not feasible.

Study treatment interruptions due to TEAEs were reported for 14 (35%) of the patients, with neutrophil count decreased (2 [5%] patients) being the only TEAE leading to treatment interruption reported in more than one patient.

A total of five (13%) patients discontinued larotrectinib due to TEAEs, of which three were related to the CNS disease itself and two were due to neurologic TEAEs (PTs dysarthria and motor dysfunction).

AESIs included AST and ALT elevation, neurologic events, and fracture events.

A total of 15 (38%) patients had TEAEs of ALT and/or AST increased, of which one was a grade 3. One patient also had the larotrectinib dose interrupted due to grade 3 ALT and/or AST increased. No patients met the Hy's Law definition of drug induced liver injury.

TRK receptors are expressed in the brain and nervous system in the postnatal period and may impact various cerebral functions. At the time of approval of larotrectinib, juvenile toxicity studies indicated a delay in sexual maturation landmarks for both sexes with a potential connection to early growth retardation. Neurologic TEAEs have also been reported for other TRK receptor inhibitors used in paediatric populations. In study 20290 and, consequently, in the PIP03 potential neurologic toxicity was closely monitored.

In the PIP03, the most common neurologic TEAE under SOC Nervous system disorders was PT headache (11 [28%] patients) and the most common TEAE under SOC Psychiatric disorders was PT insomnia (three [8%] patients). As outlined above, two patients had neurologic events that led to permanent discontinuation of larotrectinib (grade 2 TEAE of motor dysfunction and grade 3 TEAE of dysarthria, respectively). One patient had neurologic events that led to study treatment interruption (grade 1 TEAE of somnolence). The ages of these patients who discontinued larotrectinib due to neurologic TEAEs were not provided.

Fracture events have been described for other TRK receptor inhibitors used in paediatric populations and were analysed as an additional safety topic in PIP03. A total of three patients reported a TEAE of fracture (one tooth fracture grade 1, one upper limb fracture grade 2, and one wrist fracture grade 2). All TEAEs of fracture resolved without sequelae.

Overall, the safety profile reported in the palatability analysis set was in line with the results of the PIP03 SAF.

In conclusion, the safety profile of larotrectinib as reported in PIP03 was in line with the established larotrectinib safety profile. No new safety concerns related to neurodevelopment or cognitive function were identified.

However, as outlined above in section `Updated paediatric PK analysis´ previously raised concerns regarding paediatric PK data, with a substantially higher exposure (4.5-fold increase [AUC0-24 on day 1]) in the youngest children <3 months of age, remain. Thus, a potential risk of exposing young children to unnecessarily high larotrectinib doses and, consequently, greater risks of toxicity, is present. Given the role of the drug target in neurodevelopment, this is a concern.

Along with the requested updated PK data, the MAH also submitted a summary of safety data related to neurodevelopment in the 154 participants in the SCOUT study. Although these data do not show any obvious differences across age groups, the limited number of patients in each age group and the inherent developmental aspects associated with different ages makes it difficult to draw any conclusion regarding potential safety differences across ages. Moreover, it is considered that the target NTRK is involved in neurodevelopment, and the consequences of inhibition very early in life is unclear. Since available data now confirm that the exposure in the youngest age group is significantly higher than in

older children where there is more evidence of efficacy and safety, an updated PK modelled dose in children aged 1-3 months is desirable. This should be submitted in a separate variation application.

According to the MAH, the paediatric development of larotrectinib is completed with the PIP03 report. In the Cover Letter, the MAH requests that a statement indicating compliance with the application of the agreed PIP EMEA-001971-PIP03-18-M02 should be included into the Marketing Authorisation. This can, however, only be issued in the context of a variation procedure after assessment and confirmation that the relevant information is reflected in the PI. The MAH is invited to submit this request in an appropriate variation application.

3. CHMP rapporteur's overall conclusion and recommendation

☒ Fulfilled:

☐ Not fulfilled:

In view of the available data regarding the significantly higher exposure in children aged <3 months compared with older children, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

The MAH is requested to submit a separate variation with a re-evaluated dose in children aged 1-3 months, with the aim to match the exposure (primarily AUC) to older children at steady-state. In the submission, simulations of exposure should be done with a uniform body weight and age distribution. Plots of exposure versus BSA should also be presented.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. Given the notably higher exposure in the youngest children, especially in children aged 1 to 3 months (both compared with older children and adults) and the fact that the target of larotrectinib is involved in neurodevelopment, the applicant should discuss and consider whether a lower starting dose might have a better risk profile while maintaining efficacy. In relation to this, the MAH is requested to present the following additional information:

a) A clear summary of available PK-data in all children, along with all relevant demographic, sampling, and dosing information.

b) Observed PK data and the target exposure (could be model derived if PK sampling was sparse) in adults from phase 3 that exposure in children should be compared to. Please present both visual overview and tabulated results.

c) For an informative PK-assessment to be possible, a pooled population PK analysis approach is necessary, i.e., using all available data from children and adult patients. The applicant should present a summary report of the larotrectinib Population PK model, along with model evaluation and qualification of the model. The applicant should demonstrate the model's predictive capability (according to relevant guidelines) for all age groups.

For information on additional ways to present data, please also refer to EMAs M&S Q&A https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-pharmacology-and-pharmacokinetics/modelling-and-simulation-questions-and-answers.

The timetable is a 30-day response timetable without clock stop.

MAH responses to Request for supplementary information

Question 1

1. Given the notably higher exposure in the youngest children, especially in children aged 1 to 3 months (both compared with older children and adults) and the fact that the target of larotrectinib is involved in neurodevelopment, the applicant should discuss and consider whether a lower starting dose might have a better risk profile while maintaining efficacy. In relation to this, the MAH is requested to present the following additional information:

    a. A clear summary of available PK-data in all children, along with all relevant demographic, sampling, and dosing information.

    b. Observed PK data and the target exposure (could be model derived if PK sampling was sparse) in adults from phase 3 that exposure in children should be compared to. Please present both visual overview and tabulated results.

    c. For an informative PK-assessment to be possible, a pooled population PK analysis approach is necessary, i.e., using all available data from children and adult patients. The applicant should present a summary report of the larotrectinib Population PK model, along with model evaluation and qualification of the model. The applicant should demonstrate the model's predictive capability (according to relevant guidelines) for all age groups.

For information on additional ways to present data, please also refer to EMAs M&S Q&A https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-pharmacology-and-pharmacokinetics/modelling-and-simulation-questions-and-answers.

Summary of MAH answer Question 1a

A clear summary of available PK-data in all children, along with all relevant demographic, sampling, and dosing information.

The PK of larotrectinib in paediatric patients was evaluated in Study 20290 along with efficacy/safety evaluations. Study 20290 is an ongoing, multicentre, open-label, Phase 1/2 study in paediatric patients aged **from birth through 21 years** with advanced solid or primary CNS tumours. The CSR of Study 20290 will be provided with the EU Renewal Submission on 7 MAR 2025.

In total, 154 patients were enrolled, with 41 patients in Phase 1 portion and 113 patients in Phase 2 portion of the study. The details of patient demographics are presented in Table 1 stratified by the NTRK fusion status. The median age of the patients was 5.13 years, ranging from 0.1 year (<1 month) to 20.5 years, with 6 patients (4%) older than 18 years of age.

Table 1: Patient demographics in Study 20290

	NTRK Fusion N=146	Non-*NTRK* Fusion N=8	Total N=154
Age (years)			
Median	4.96	14.13	5.13
Range	0.1, 20.5	3.0, 17.6	0.1, 20.5
Age category, n (%)			
<3 months	13 (9)	0	13 (8)
3 months to <1 year	23 (16)	0	23 (15)
1 to <2 years	11 (8)	0	11 (7)
2 to <6 years	34 (23)	2 (25)	36 (23)
6 to <12 years	37 (25)	1 (13)	38 (25)
12 to <16 years	16 (11)	3 (38)	19 (12)
≥16 years	12 (8)	2 (25)	14 (9)
Gender, n (%)			
Female	67 (46)	4 (50)	71 (46)
Male	79 (54)	4 (50)	83 (54)
Race, n (%)			
White	89 (61)	2 (25)	91 (59)
Asian	28 (19)	1 (13)	29 (19)
Other	17 (12)	4 (50)	21 (14)
Black or African American	2 (1)	1 (13)	3 (2)
Native Hawaiian or Other Pacific Islander	1 (<1)	0	1 (<1)
Multiple	1 (<1)	0	1 (<1)
Patient declined to state	8 (5)	0	8 (5)
Ethnicity, n (%)			
Non-Hispanic or Latino	124 (85)	4 (50)	128 (83)
Hispanic or Latino	12 (8)	3 (38)	15 (10)
Declined to state	10 (7)	1 (13)	11 (7)
Body weight (kg)			
Median	18.05	44.28	19.00
Range	3.2, 89.2	14.7, 82.7	3.2, 89.2
BSA (m^2)			
Median	0.73	1.34	0.76
Range	0.2, 2.1	0.6, 2.0	0.2, 2.1

Abbreviations: BSA = body surface area; N = total number of patients (100%); n = number of patients in category/with event; *NTRK* = neurotrophic tyrosine receptor kinase

Notes: Due to rounding, percentages may sometimes not add up to 100 (e.g., for age categories).
Percentages are based on the number of patients (N) specified in the column header.
Baseline values are those measured closest to but not after the first dose of larotrectinib.

The initial starting dose of larotrectinib in early cohorts of the Phase 1 portion was based on the dose in adults (i.e., 100 mg BID) and PK modelling (SimCyp®) for doses in paediatric patients that was predicted to equal the exposure achieved in adult patients. The doses in later cohorts in Phase 1 and Phase 2 were selected based on the observations from early cohorts. Several dose levels were employed in the study. The starting dose levels are summarized in Table 2. The recommended Phase 2 dose for paediatric patients was 100 mg/m2 BID (not exceeding 100 mg BID). Larotrectinib was administered as oral capsule or liquid solution.

Table 2: Starting dose levels of larotrectinib in Study 20290

Level	Pediatric Dose	Adult Equivalent Dose	% of Adult Dose of 100 mg BID	Cycle Length	Duration of Dosing
-2	4.8 to 27.5 mg/m^2 BID	50 mg BID	50%	One cycle = 28 days continuous dosing	Dosing continues until progressive disease, unacceptable toxicity, or other reason for treatment discontinuation
-1	7.2 to 41.3 mg/m^2 BID	75 mg BID	75%		
1	9.6 to 55 mg/m^2 BID	100 mg BID	100%		
2	17.3 to 120 mg/m^2 BID	150 mg BID	150%		
3 [a]	100 mg/m^2 BID	.	.		

Abbreviations: BID = twice daily

a Patients enrolled in the Phase 1 Dose-Escalation Cohort 3, Phase 1 Dose-Expansion Cohort, and Phase 2 Cohorts did not follow the dose level tables referenced in the current protocol; these patients were dosed based on the calculated body surface area on Day 1 of each cycle visit

Blood samples were collected on Cycle 1 Day 1 and Cycle 4 Day 1 at various time points as shown in Table 3.

Table 3: PK blood sampling schedule for Study 20290

Phase	Cohorts	Visit	PK Time Points
1	Escalation Cohort 1, Escalation Cohort 2	Cycle 1 Day 1	1, 4 and 12 hours postdose
		Cycle 4 Day 1	Predose, 1 and 4 hours postdose
	Escalation Cohort 3	Cycle 1 Day 1	0.5, 1, 2, 4, 8, 12 hours postdose
		Cycle 4 Day 1	Predose, 0.5, 1, 2, 4 hours postdose
	Dose Expansion	Cycle 1 Day 1	0.5 [a], 1, 2 [a], 4, 6 [a] or 8 [a], 12 [a] hours postdose
		Cycle 4 Day 1	Predose, 0.5[a], 1, 2[a], 4, 6[a] or 8[a] hours postdose
2	Cohort 1, Cohort 2, Cohort 3	Cycle 1 Day 1	0.5 [a], 1, 2 [a], 4, 6 [a] or 8 [a], 12 [a] hours postdose
		Cycle 4 Day 1	Predose, 0.5 [a], 1, 2 [a], 4, 6 [a] or 8 [a] hours postdose

Abbreviations: PK = pharmacokinetic(s)

a Patients within the cohort followed various PK sampling schedule and flagged sample was not collected for the majority of patients.

Patients who received at least one dose of study drug and had at least one valid plasma PK concentration were included in the concentration analysis, which includes (Module 5.3.3.5, Study 20290, Report BAYE-LARO-6177, Section 5.1):

a. Phase 1: 40 patients on Cycle 1 Day 1 and 21 patients on Cycle 4 Day 1

b. Phase 2: 112 patients on Cycle 1 Day 1 and 104 patients on Cycle 4 Day 1

Patients who received at least one dose of study drug and had sufficient plasma concentration data (i.e., at least 5 postdose PK samples) were included in PK parameter evaluation, which includes:

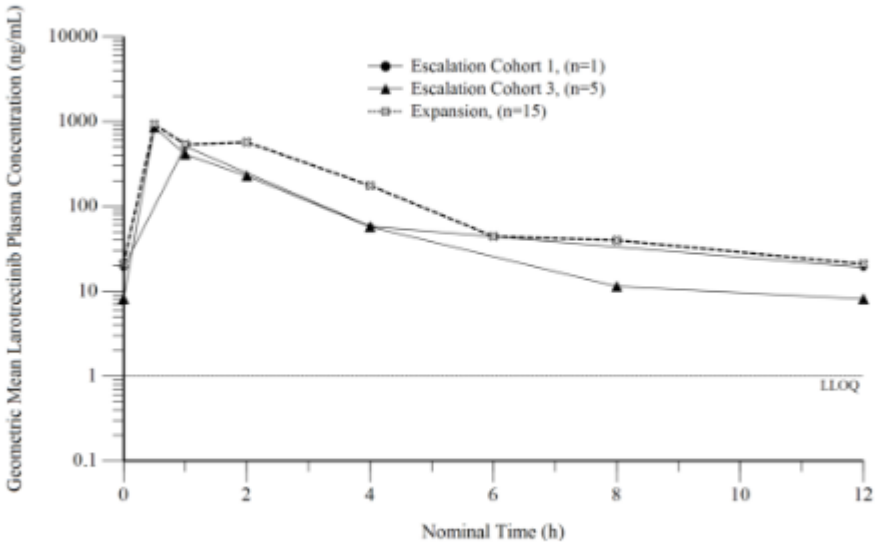
c. Phase 1: 15 patients on Cycle 1 Day 1 and 11 patients on Cycle 4 Day 1

d. Phase 2: 33 patients on Cycle 1 Day 1 and 27 patients on Cycle 4 Day 1

Geometric mean plasma larotrectinib concentration–time profiles following multiple BID administrations of larotrectinib on Cycle 4 Day 1, which is considered as steady state, are presented by cohort on semi-logarithmic scales for all Phase 1 and Phase 2 patients in Figure 1 and Figure 2, respectively. Geometric mean plasma larotrectinib concentration–time profiles on Cycle 4 Day 1 for Phase 2 patients are also presented by paediatric age group on semi-logarithmic scale in Figure 3. Following first (Cycle 1 Day 1) or multiple (Cycle 4 Day 1) oral administrations, larotrectinib was rapidly absorbed, with geometric mean maximal concentration achieved at 0.5 to 1 hour for most cohorts, regardless of the study phase (Phase 1 or Phase 2). Geometric mean plasma larotrectinib concentration then decreased afterward, with detectable level at 12 hours postdose. The decrease follows similar pattern in semi-

logarithmic scales for different age groups and tumour types, suggesting similar elimination rate. Geometric mean plasma larotrectinib concentration profile was similar among all Phase 2 cohorts on Cycle 4 Day 1, overlapping at multiple time points, suggesting no effect of different tumour types on larotrectinib PK profile (Figure 2). As shown in Figure 3, among Phase 2 paediatric age groups on Cycle 4 Day 1, the patients aged 1 to 3 months (N=10) tended to show the highest geometric mean plasma larotrectinib exposure while other paediatric age groups appeared to have comparable geometric mean plasma larotrectinib profiles. Minimal accumulations were observed as the geometric mean plasma larotrectinib concentrations at predose on Cycle 4 Day 1 following multiple doses were <5% of maximal concentration values in the corresponding profile. Plasma larotrectinib concentrations were associated with moderate to very high variability, with geometric CV% ranging between 30.3 and 680%.

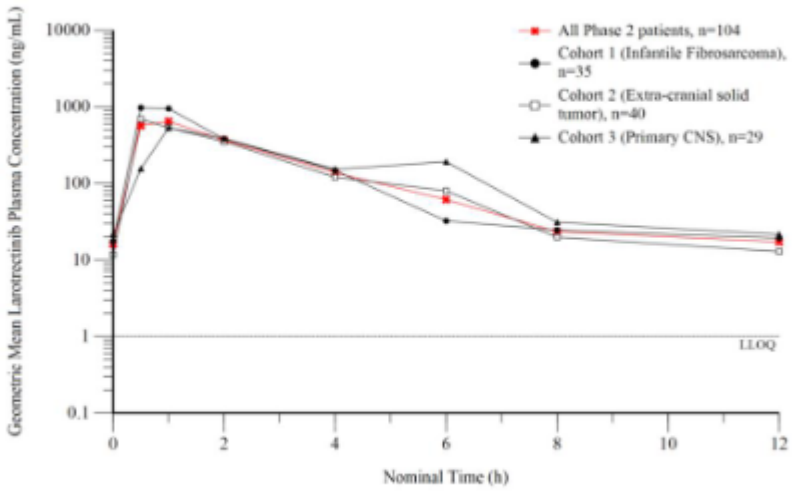
Figure 1: Geometric Mean Plasma Concentrations of Larotrectinib Following Multiple Oral Administrations of Larotrectinib BID in Phase 1 Pediatric Patients – Cycle 4 Day 1 (Semi-Logarithmic Scale) in Study 20290



Abbreviations: BID = twice daily; LLOQ = lower limit of quantification; n = number of patients in category/with event

Notes: The semi-logarithmic plot displays the LLOQ of 1.00 ng/mL. The 12-hour concentration was imputed from predose concentration.

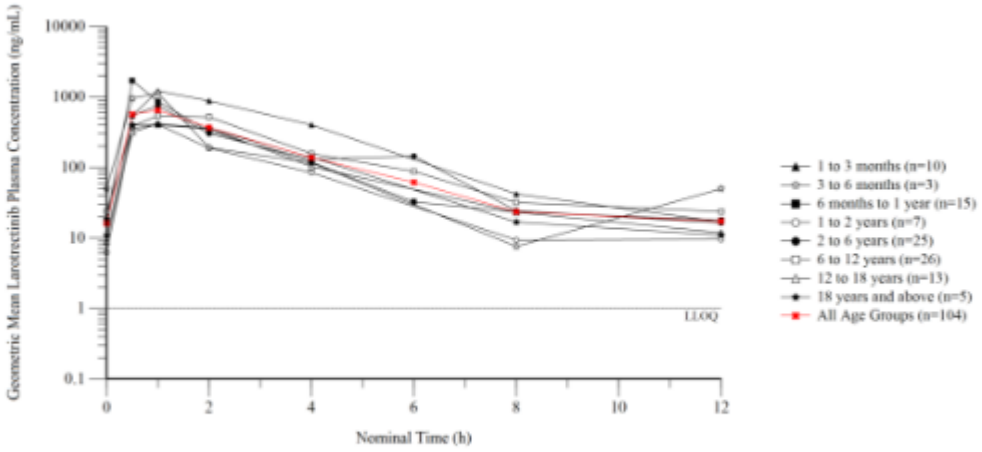
Figure 2: Geometric Mean Plasma Concentrations of Larotrectinib Following Multiple Oral Administrations of Larotrectinib BID in Phase 2 Pediatric Patients – Cycle 4 Day 1 (Semi-Logarithmic Scale) in Study 20290



Abbreviations: BID = twice daily; CNS = central nervous system; LLOQ = lower limit of quantification; n = number of patients in category/with event

Notes: The 12-hour concentration was imputed from predose concentration. The semi-logarithmic plot displays the LLOQ of 1.00 ng/mL.

Figure 3: Geometric Mean Plasma Concentrations of Larotrectinib Following Multiple Oral Administrations of Larotrectinib BID in Phase 2 Pediatric Patients by Age Group – Cycle 4 Day 1 (Semi-Logarithmic Scale) in Study 20290



Abbreviations: BID = twice daily; LLOQ = lower limit of quantification; n = number of patients in category/with event

Notes: The 12-hour concentration was imputed from predose concentration. The semi-logarithmic plot displays the LLOQ of 1.00 ng/mL.

Summary of plasma larotrectinib PK parameters for patients in Phase 1 are presented by cohort in Table 4 for both Cycle 1 Day 1 and Cycle 4 Day 1. Of the 40 Phase 1 patients with available Cycle 1 Day 1 data, only 15 patients (N=9 from dose-escalation Cohort 3; N=6 from dose-expansion Cohort) had sufficient (i.e., at least 5) number of plasma concentrations available and were used to obtain PK parameters on Cycle 1 Day 1. Of the 21 Phase 1 patients with available Cycle 4 Day 1 data, only 11 patients (N=5 from dose-escalation Cohort 3; N=6 from dose-expansion Cohort) had sufficient (i.e., at least 5) number of plasma concentrations and were used to obtain PK parameters. The median Tmax ranged from 0.50 to 1.27 hours for both Cycle 1 and Cycle 4, suggesting fast absorption. The geometric mean values of dose-normalized AUC were similar for Escalation Cohort 3 on Cycle 1 Day 1,

Escalation Cohort 3 on Cycle 4 Day 1, and Expansion cohort on Cycle 4 Day 1, suggesting minimal accumulation and no difference of exposure in different tumour types. The geometric mean dose-normalized AUC values for Expansion cohort on Cycle 1 Day 1 are lower than the corresponding dose-normalized AUC values of the same cohort on Cycle 4 Day 1; the number of patients with available data may be one of the reasons for the difference. Nevertheless, the larotrectinib exposure (both dose-normalized Cmax and AUC) are associated with high variability, with (geometric CV% ranging between 61.9 and 188.0%).

Table 4: Geometric Mean Plasma PK Parameters of Larotrectinib in Phase 1 Pediatric Patients Following a Single Oral Administration of Larotrectinib – Cycle 1 Day 1, and Following Multiple Oral Administrations of Larotrectinib BID – Cycle 4 Day 1 in Study 20290

		Phase 1 Cohorts	
PK Parameters [a]	Units	Escalation Cohort 3 N=9	Expansion Advanced solid or primary CNS N=6
		Cycle 1, Day 1	
T_{max}[b]	h	0.58 (0.03, 1.97);9	1.27 (0.50, 2.27);6
AUC_{0-12}/Dose	h*ng/mL/mg	31.0 (142.8);9	12.0 (188.0);2
AUC_{0-last}/Dose	h*ng/mL/mg	31.0 (142.8);9	19.4 (123.6);6
C_{max}/Dose	ng/mL/mg	12.5 (116.8);9	7.53 (179.5);6
		Escalation Cohort 3 N=5	Expansion Advanced solid or primary CNS N=6
		Cycle 4, Day 1	
T_{max}[b]	h	0.50 (0.48, 1.98);5	0.78 (0.48, 2.17);6
AUC_{0-12} [c]/Dose	h*ng/mL/mg	28.8 (77.5);5	34.5 (62.4);6
AUC_{0-last}/Dose	h*ng/mL/mg	27.7 (78.1);5	32.4 (61.9);6
C_{max}/Dose	ng/mL/mg	21.3 (67.9);5	15.3 (65.6);6

Abbreviations: AUC_{0-12} = area under the plasma concentration-time curve from time 0 to 12 hours; AUC_{0-last} = area under the plasma concentration-time curve from time 0 to last measurable concentration; BID = twice daily; C_{max} = maximum concentration; CNS = central nervous system; CV = coefficient of variation; Max = maximum; Min = minimum; N = total number of patients (100%); PK = pharmacokinetic(s); T_{max} = time to reach maximum concentration

a Geometric mean (Geometric CV%);N

b Median (Min; Max);N

c The 12-hour concentration was imputed from predose concentration for the calculation of AUC_{0-12}.

Summary of plasma larotrectinib PK parameters for all Phase 2 patients are presented by age group in Table 5 for Cycle 1 Day 1, and in Table 6 for Cycle 4 Day 1. Summary of plasma larotrectinib PK parameters in Phase 2 are also presented by cohort in Table 7 for Cycle 4 Day 1. Of the 112 Phase 2 patients with available Cycle 1 Day 1 data, only 33 patients had sufficient number (i.e., at least 5) of plasma concentrations and were used to obtain PK parameters on Cycle 1 Day 1. Of the 104 Phase 2 patients with available Cycle 4 Day 1 data, only 27 patients had sufficient number (i.e., at least 5) of plasma concentrations and were used to obtain PK parameters on Cycle 4 Day 1. Box plots of Cycle 4 Day 1 plasma larotrectinib dose-normalized PK parameters (Cmax, AUC0-4) are presented for all Phase 2 patients by age group in Figure 4. Consistent with what has been observed in Phase 1, the median Tmax in Phase 2 ranged from 0.50 to 1.56 hours for both Cycle 1 and Cycle 4, suggesting fast absorption (Table 5 and Table 6). Although it is hard to make a fair comparison due to very limited number of patients in each age group and different numbers of patients between Cycle 1 and Cycle 4 for the same age group, it appears that the exposures (geometric mean AUC) on Cycle 1 Day 1 and Cycle 4 Day 1 are generally similar for the same age group, suggesting limited accumulation. As shown

in Figure 4, younger age groups (e.g., <1 year old) appear to be associated with high variability and higher exposure compared to older age groups (e.g., >1 year old).

Summary of MAH answer Question 1b

Observed PK data and the target exposure (could be model derived if PK sampling was sparse) in adults from phase 3 that exposure in children should be compared to. Please present both visual overview and tabulated results.

While Study 20290 is an open-label, Phase 1/2 study in paediatric patients aged from birth through 21 years, Study 20289 is a Phase 2, open-label "basket" study in patients 12 years of age or older. The larotrectinib concentrations from these two studies are compared to evaluate the exposure in paediatrics compared to that in adults. The PK sampling timepoints for Study 20289 (0 hr [predose], 1 hr, and 4 hr postdose on Cycle 1 Day1, Cycle 1 Day 8, Cycle 3 Day 1, and Cycle 5 Day 1) were different from those in Study 20290 (Table 3). However, there are common timepoints in both studies: PK samples were obtained at 0 hr (predose), 1 hr, and 4 hr postdose at steady state in both studies. These data are listed in Table 8 by different age groups for patients receiving the recommended dose (100 mg/m2 up to 100 mg BID) from both studies for direct comparison. Among these data following multiple doses of larotrectinib, 0 hr concentration is the Cmin, and 1 hr concentration should be close to Cmax value considering the fast absorption of larotrectinib with Tmax achieved at approximately 1 hr after dosing as stated in the label. Meanwhile, the Box Plots of the same data are presented in Figure 5 and Figure 6 for 1 hr and 4 hr larotrectinib concentrations, respectively, across different age groups for patients receiving the recommended dose (100 mg/m2 up to 100 mg BID). Compared to the data presented in Section 1.1, the data here provided direct comparison on actual larotrectinib concentrations observed with all available data from patients across different age groups in Phase 2 Studies 20289 and 20290. Figure 5 (1 hr concentration after multiple doses) represents the steady state Cmax value comparison across different age groups. As demonstrated in Figure 5, the median larotrectinib concentration value for the youngest patient population is higher than that for the older age groups; however, the range of the concentration is mostly overlapping with the range in the other age groups with only one outlier high value. For the concentration at later timepoint at steady state (4 hr concentration after multiple doses) shown in Figure 6 the range for the youngest patient population contains entirely the range for the adults.

Table 8: Summary statistics for concentrations of larotrectinib (ng/mL) in PLASMA (pharmacokinetic analysis set - all patients with 100 mg or 100 mg/m^2 BID) by age

					Larotrectinib Concentration (ng/mL)								
Age group	Analysis Visit [a]	Time point	n	n ≥ LLOQ	Geom. Mean	Geom. SD	Geom. CV(%)	Arithm. Mean	Arithm. SD	Arithm. CV(%)	Min	Median	Max
<3 month	Cycle 1 Day 1	1H	11	11	1910	1.65	53.10	2130	1070	50.17	727	1700	4700
		4H	11	11	1120	1.61	50.30	1250	676	53.95	639	1010	2880
	Cycle 4 Day 1	0H	10	10	15.8	1.93	73.54	18.6	9.52	51.16	5.63	20.3	29.8
		1H	10	10	1160	1.68	55.90	1340	912	68.23	585	1180	3770
		4H	8	8	328	2.11	86.17	404	261	64.66	79.0	352	921
3 to <6 months	Cycle 1 Day 1	1H	4	4	1160	2.23	95.03	1470	1080	73.80	512	1260	2840
		4H	4	4	110	2.83	139.43	170	195	114.57	38.7	91.0	460
	Cycle 4 Day 1	0H	4	4	38.6	6.50	567.84	145	250	172.29	6.55	27.1	520
		1H	4	4	781	3.26	174.30	1240	1180	95.17	253	998	2720
		4H	4	4	113	2.01	79.43	132	72.5	54.78	43.5	141	204
6 to <12 months	Cycle 1 Day 1	1H	17	17	1080	2.48	113.02	1580	1430	90.49	292	957	5340
		4H	17	17	196	3.67	210.67	384	448	116.65	16.6	230	1520
	Cycle 4 Day 1	0H	17	17	16.1	4.10	251.40	101	350	347.99	1.72	13.6	1460
		1H	17	17	797	1.94	74.57	987	694	70.37	366	920	2850
		4H	17	17	121	2.37	105.16	170	152	89.60	25.2	131	621
1 to <2 years	Cycle 1 Day 1	1H	9	9	655	1.83	66.11	755	391	51.84	208	768	1470
		4H	9	9	63.2	4.32	273.88	214	456	213.00	9.71	38.1	1420
	Cycle 4 Day 1	0H	7	6	6.26	5.40	402.44	23.0	46.4	201.75	<LLOQ	5.81	128
		1H	7	7	409	2.40	107.60	614	747	121.68	157	393	2280
		4H	7	7	80.4	4.86	334.33	173	192	111.42	6.40	136	563
2 to <6 years	Cycle 1 Day 1	1H	32	32	631	2.30	99.79	827	648	78.36	39.6	713	3420
		4H	31	31	69.4	2.46	111.41	93.0	68.1	73.22	2.66	75.7	305
	Cycle 4 Day 1	0H	30	30	17.6	2.16	90.29	25.8	36.1	139.64	4.38	15.6	204
		1H	28	28	779	1.82	65.95	900	462	51.33	108	778	2190
		4H	29	29	136	2.09	84.87	174	126	72.75	30.2	164	575

Table 8: Summary statistics for concentrations of larotrectinib (ng/mL) in PLASMA (pharmacokinetic analysis set - all patients with 100 mg or 100 mg/m² BID) by age

Age group	Analysis Visit [a]	Time point	n	n ≥ LLOQ	Larotrectinib Concentration (ng/mL) Geom. Mean	Geom. SD	Geom. CV(%)	Arithm. Mean	Arithm. SD	Arithm. CV(%)	Min	Median	Max
6 to <12 years	Cycle 1 Day 1	1H	36	36	525	2.83	139.36	819	853	104.14	42.4	635	3980
		4H	36	36	157	2.42	108.61	243	282	116.28	39.0	143	1110
	Cycle 4 Day 1	0H	31	31	21.7	2.50	114.59	56.5	190	336.87	7.78	22.3	1080
		1H	32	32	547	3.00	152.69	791	541	68.38	16.1	736	2360
		4H	32	32	155	1.95	74.68	188	110	58.61	35.9	169	415
12 to <18 years	Cycle 1 Day 1	1H	29	29	489	2.17	90.48	610	360	59.02	66.5	556	1740
		4H	28	28	125	2.11	86.04	165	151	91.30	33.9	116	789
	Cycle 4 Day 1	0H	22	19	8.32	3.54	198.96	13.2	10.0	75.78	<LLOQ	11.1	37.1
		1H	23	23	435	2.43	109.69	568	348	61.37	27.0	515	1410
		4H	22	22	117	1.79	63.88	135	67.2	49.71	31.7	125	254
≥18 years	Cycle 1 Day 1	1H	214	214	443	2.95	149.26	644	504	78.17	1.48	557	3360
		4H	214	213	164	2.68	128.26	251	267	106.53	<LLOQ	161	2260
	Cycle 4 Day 1	0H	172	158	11.2	4.19	260.13	30.3	73.3	241.86	<LLOQ	11.2	739
		1H	172	171	374	2.61	122.56	492	311	63.29	<LLOQ	454	2200
		4H	169	169	133	2.13	87.71	179	174	97.38	6.32	139	1480
All Ages in the Study	Cycle 1 Day 1	1H	352	352	523	2.84	140.80	780	721	92.48	1.48	597	5340
		4H	350	349	154	2.91	145.60	265	341	128.56	<LLOQ	147	2880
	Cycle 4 Day 1	0H	293	275	12.7	3.79	221.54	36.4	122	335.89	<LLOQ	13.2	1460
		1H	293	292	466	2.62	123.50	640	496	77.39	<LLOQ	515	3770
		4H	288	288	135	2.18	91.24	181	162	89.70	6.32	145	1480

Abbreviations: Arithm. = arithmetic; BID = twice daily; CV = coefficient of variation; Geom. = geometric; Max = maximum; Min = minimum; LLOQ = lower limit of quantification; n = number of patients with event/in category; NC = not calculated; SD = standard deviation

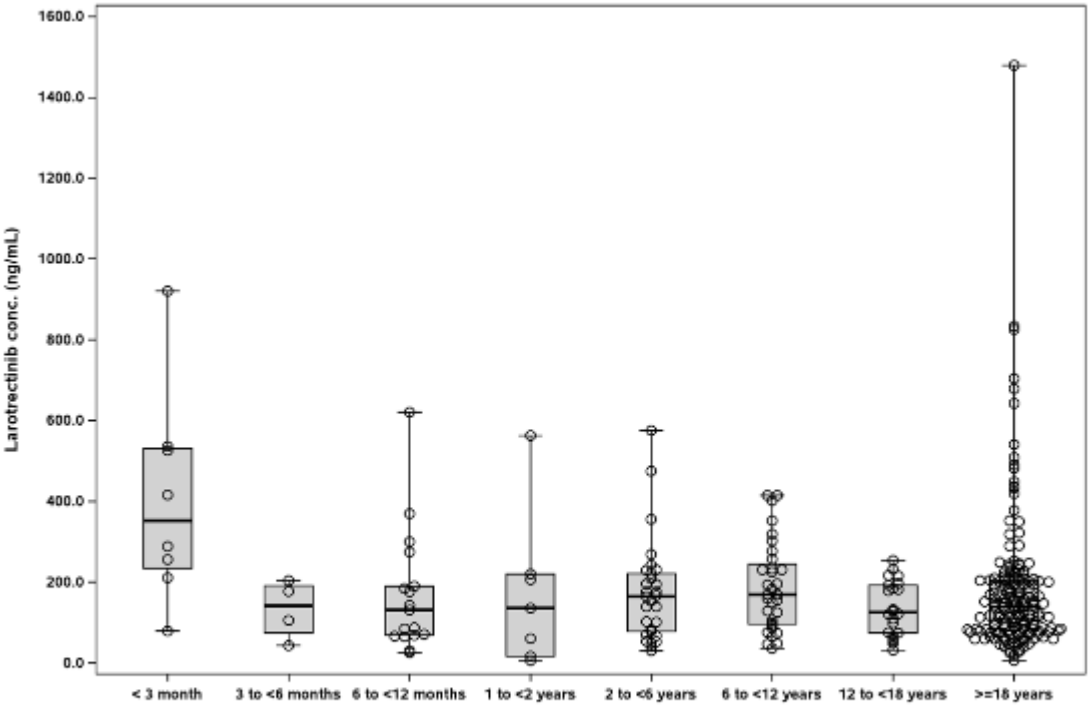
Notes: LLOQ values are 1 5 20.

No missing values.

Summary statistics are calculated only for data ≥3, except from min. and max.

a For Study 20289, values available from Cycle 3 or Cycle 5 were used instead of Cycle 4.

Figure 6: Box Plot of Larotrectinib Concentration at 4 Hours at steady state (pharmacokinetic analysis set - all patients with 100 mg or 100 m g/m² BID) by age



Abbreviations: BID = twice daily

Box: 25th and 75th percentile; horizontal line: median; vertical lines extend from the box as far as the data extends, including outliers.

For Study 20289, concentration data available from Cycle 3 or Cycle 5 were used. For Study 20290, concentration data from Cycle 4 were used.

As PK samplings for most patients in Study 20289 and Study 20290 are sparse samplings, a population PK approach was also applied to estimate the effect of age on larotrectinib exposure. Please see the answer for Question 1c (Section 1.3) for details.

Summary of MAH answer Question 1c

For an informative PK-assessment to be possible, a pooled population PK analysis approach is necessary, i.e., using all available data from children and adult patients. The applicant should present a summary report of the larotrectinib Population PK model, along with model evaluation and qualification of the model. The applicant should demonstrate the model's predictive capability (according to relevant guidelines) for all age groups.

Effect of age on larotrectinib Cmax and AUC based on data from final population PK model

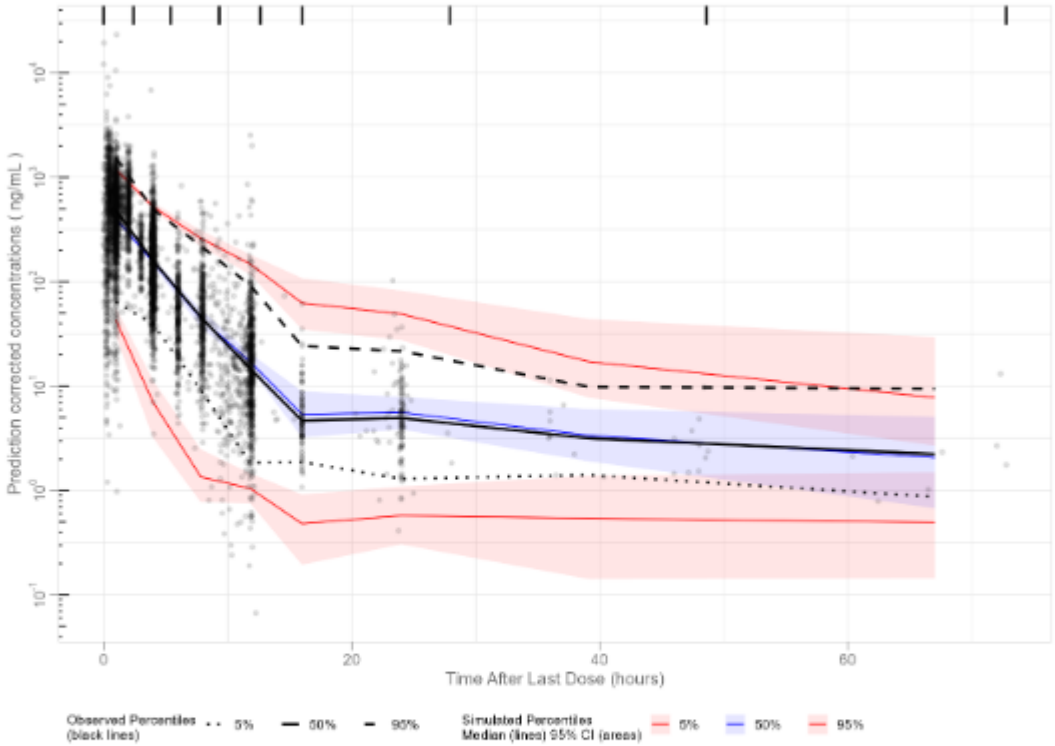
The PK data from Studies 20289 and 20290 were analyzed together with data from previous larotrectinib clinical Studies 20291 (LOXO-TRK-16007), 20292 (LOXO-TRK-16009), 20295 (LOXO-TRK-16012), 20288 (LOXO-TRK-14001), 20289 (LOXO-TRK-15002), 20290 (LOXO-TRK-15003), and 20381 using a population approach. The population PK model parameters were estimated using 5768 PK samples from 526 subjects (including healthy volunteers and patients) from these studies. Among pediatric patients, there were 12 patients in the 1 to <3 months age group (including one patient of 18 days), 4 patients in the 3 to <6 months age group, 19 patients in the 6 to <12 months age group, 11 patients in the 1 to <2 years age group, 37 patients in the 2 to <6 years age group, 38 patients in the 6 to <12 years age group, and 32 patients in the 12 to <18 years age group. In addition, intrinsic and extrinsic factors that influence larotrectinib exposure were identified. The final population PK model was then used to simulate larotrectinib exposures at the recommended therapeutic dosing regimen for adults and paediatric patients.

The final population PK model for larotrectinib following oral administration was a 2-compartment disposition model with sequential zero-order and first-order absorption. Between-subject variability terms were included on CL/F, Vc/F, ka, and Dur. The residual error model included a proportional error term. Plasma samples that BLQ were set to missing for the final model. The intrinsic factors albumin, total bilirubin, age (especially very young age), body weight (especially very low body weight), and patient status (healthy versus patient) influenced the PK of larotrectinib.

Clearance parameters (CL/F and Q/F) and volume of distribution parameters (Vc/F and VpF) were scaled using body weight (normalized to 70 kg) and fixed allometric exponents (0.75 for clearance parameters and 1.0 for volume parameters). Larotrectinib CL/F maturation in paediatric subjects was captured by a sigmoidal function based on postnatal age (in years) with a fixed hill coefficient of 1. At ~4.4 months (95% CI: [2.6; 7.5]) of age, 50% of the adult (18 years old) CL/F levels were reached.

The final population PK model accurately describes the observed concentration–time profiles for all age categories in the analysis dataset (Figure 7 and Figure 8). The youngest age groups (1 to <3 months [N=12] and 3 to <6 months [N=4]) had the least amount of data and the most variability as shown by the ETA CL/F goodness of fit plots. This limited the ability of the model to estimate a hill coefficient for the maturation function with good precision, as this is mostly supported by data below 1 year of age. The model did not show any age-based bias among the various diagnostics, and prediction-corrected VPCs demonstrated concordance between observed data and model-based simulations (Figure 7 and Figure 8). Taken together, these results suggest that the final population PK model is adequate for simulation of exposure of paediatric and adult patients.

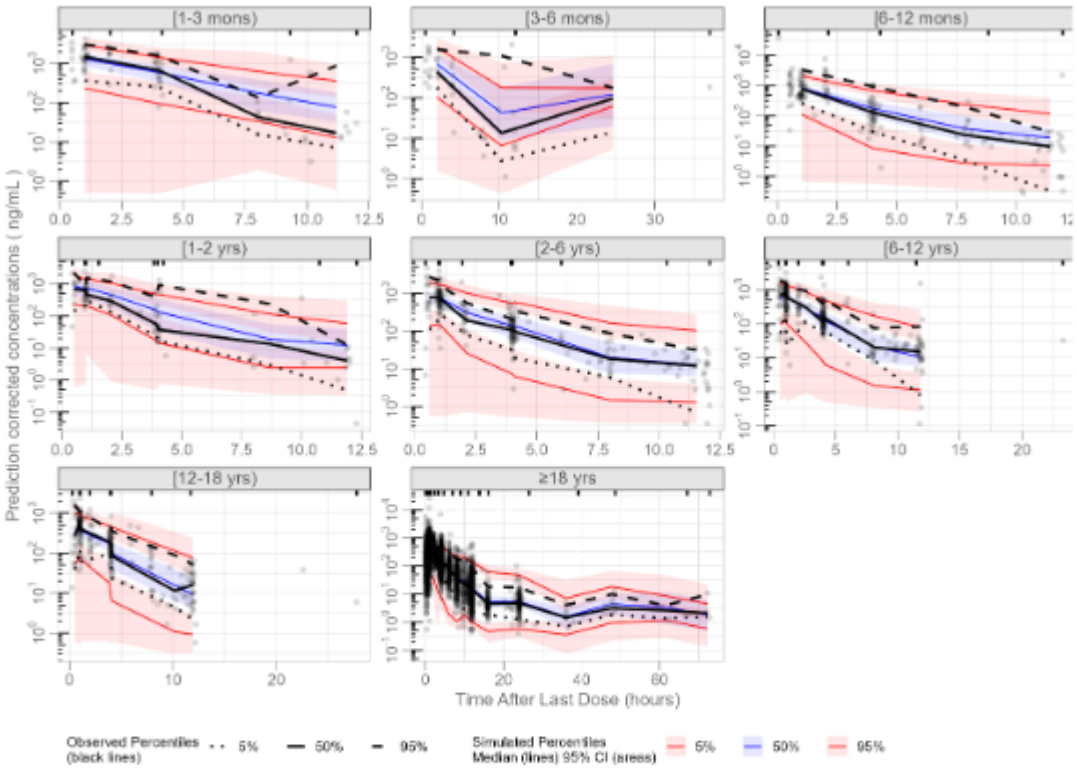
Figure 7: Prediction-Corrected VPC for the Final Population PK Model for Larotrectinib



Abbreviations: CI = confidence interval; PK = pharmacokinetic(s); VPC = Visual Predictive Check

Notes: The black dots represent prediction-corrected observed data. The black solid line represents the median of the prediction-corrected observed data. The black dotted and dashed lines represent the 5th and 95th percentiles of the prediction-corrected observed data per time-binned interval respectively. The blue solid line represents the median of the prediction-corrected simulation data. The red solid lines represent the 5th and 95th percentiles of the prediction-corrected simulation data per time-binned interval. The red shaded areas represent the 90% prediction interval for the 5th and 95th percentiles of the predicted data. The blue shaded areas represent the 90% prediction interval for the median of the predicted data.

Figure 8: Prediction-Corrected VPC for the Final Population PK Model for Larotrectinib Stratified by Age Group



Abbreviations: CI = confidence interval; PK = pharmacokinetic(s); VPC = Visual Predictive Check
Notes: The black dots represent prediction-corrected observed data, the black solid line represents the median of the prediction-corrected observed data. The black dotted and dashed lines represent the 5th and 95th percentiles of the prediction-corrected observed data respectively. The blue solid line represents the median of the prediction-corrected simulation data. The red solid lines represent the 5th and 95th percentiles of the prediction-corrected simulation data. The red shaded areas represent the 90% prediction interval for the 5th and 95th percentiles of the predicted data. The blue shaded areas represent the 90% prediction interval for the median of the predicted data.

Table 9 shows the effect of age from the final population PK model on larotrectinib Cmax and AUC by age categories. Figure 9 shows the simulated larotrectinib exposure versus age in paediatric patients from the final population PK model at the recommended therapeutic dosing regimen. Consistent with what had been reported in previous submission, the youngest age group (<3 months of age) is associated with high exposure and large variability compared to adult patients. Previous exploratory exposure–response analysis indicated that none of the safety endpoints tested were driven by larotrectinib exposure.

Table 9: Impact of Covariates from Final Population PK Model on Larotrectinib Maximum Concentration and Total Exposure by Age Categories

	$C_{max,ss}$ [a]		AUC_{ss} [a]	
Contrast	Geometric mean ratio	[90% CI]	Geometric mean ratio	[90% CI]
1–<3 months [b] vs. ≥18 years	3.22	[2.63, 3.95]	4.52	[3.46, 5.91]
3–<6 months vs. ≥18 years	2.97	[2.09, 4.21]	3.22	[2.04, 5.1]
6–<12 months vs. ≥18 years	2.11	[1.78, 2.5]	1.69	[1.36, 2.11]
1–<2 years vs. ≥18 years	1.64	[1.33, 2.03]	1.13	[0.86, 1.5]
2–<6 years vs. ≥18 years	1.59	[1.41, 1.8]	1.06	[0.91, 1.24]
6–<12 years vs. ≥18 years	1.29	[1.14, 1.45]	1.17	[1, 1.36]
12–<18 years vs. ≥18 years	0.91	[0.8, 1.03]	0.82	[0.69, 0.96]

Abbreviations: AUC_{ss} = area under the plasma concentration-time curve (at steady-state); BID = twice daily; BSA = body surface area; CI = confidence interval; $C_{max,ss}$=maximum drug concentration at steady-state; PK = pharmacokinetic(s)

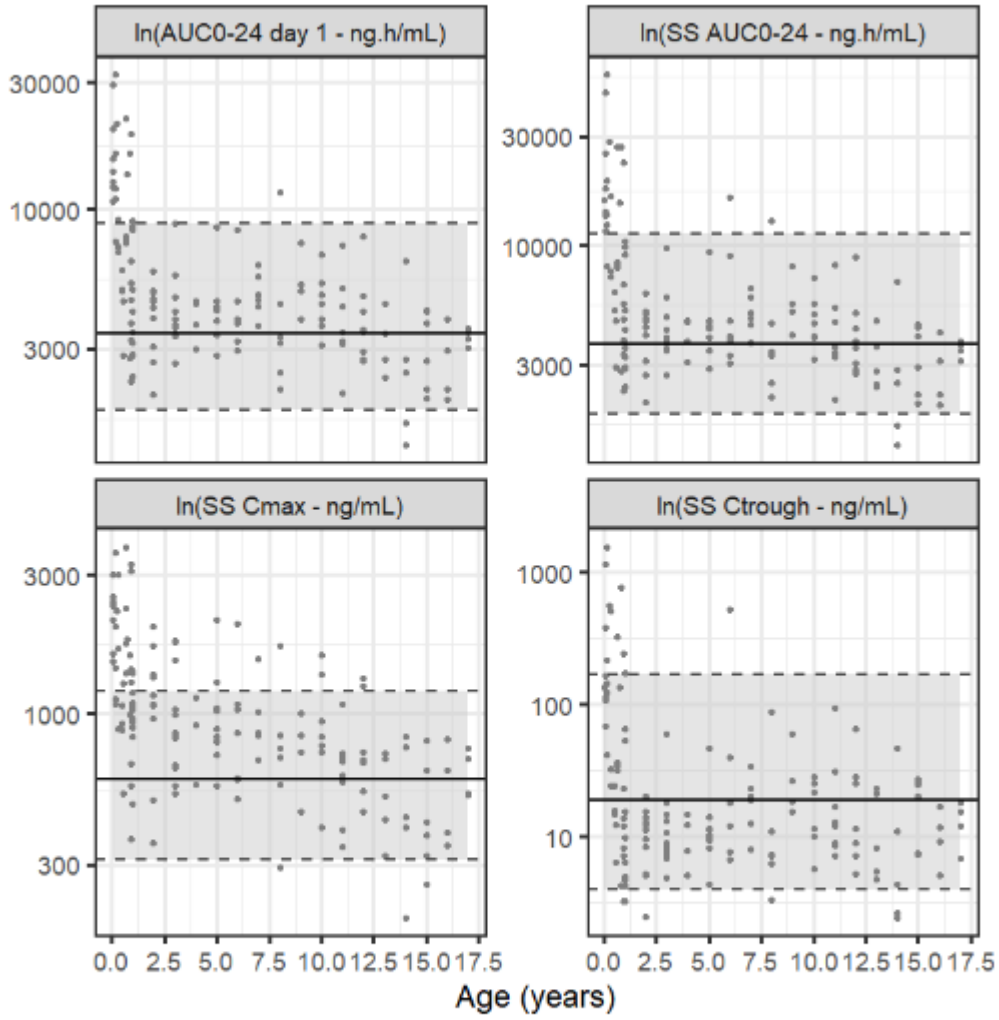
Notes: AUC and C_{max} values were determined from simulated larotrectinib concentration-time data at steady-state using subjects included in the population PK dataset and the associated individual subject post-hoc PK parameters with the recommended therapeutic dose in adults of 100 mg larotrectinib BID, and in pediatrics of 100 mg/m^2 larotrectinib BID up to a maximum dose of 100 mg larotrectinib BID. Geometric mean ratio and 90% CI were calculated for each comparison of test divided by reference, normalized to a 100 mg dose. The age covariate included only patients.

a Actual BSA-based dosing regimen.

b In the 1–<3 months age category, there was one individual with an age of 18 days included.

The final population PK model for larotrectinib was used to simulate exposures for the proposed therapeutic dosing regimen for adults and paediatrics. The proposed therapeutic dose in adults is 100 mg larotrectinib BID, and in paediatrics is 100 mg/m2 larotrectinib BID up to a maximum dose of 100 mg larotrectinib BID. Simulations were performed considering both between subject random variability and the uncertainty in the parameter estimates. Individual simulation subjects (N=1000 per age group) were generated as described in Table 10. Using the simulation subjects (N=8000 subjects in total), individual PK parameter was generated using the typical parameter estimates and the variance-covariance matrix from the final population PK model. A total of 100 replicates were prepared for each set of 8000 simulation subjects. For each replicate, a typical PK parameter was randomly selected from the uncertainty associated with the parameters, and then individual PK parameters were generated by randomly sampling from the variance-covariance matrix for each simulation subject. This resulted in 100 sets of 8000 simulation subjects that were used for the simulations. Simulations were performed up to steady-state. The simulated exposure parameters grouped by age are presented in Figure 9 and Figure 20.

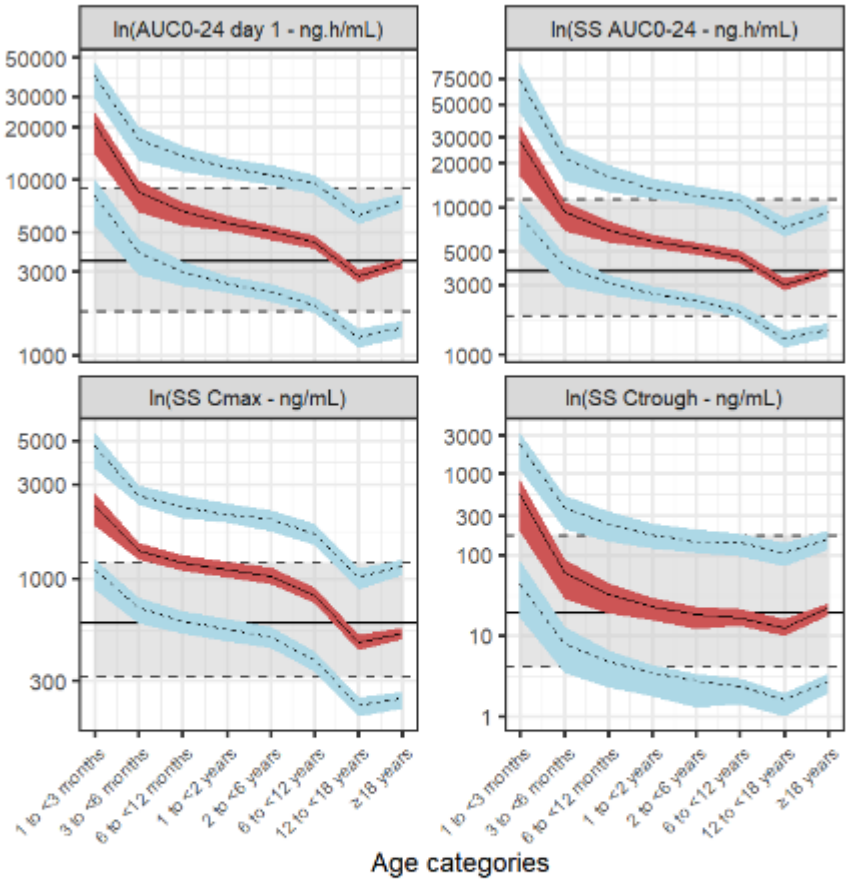
Figure 9: Simulated Larotrectinib Exposure versus Age from Pediatric Subjects in the Final Population PK Model with the Recommended Therapeutic Dosing Regimen



Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from 0 to 24 hours; C_{max} = maximum concentration; Ctrough = trough concentration; ln = natural logarithm; PK = pharmacokinetic(s); SS = steady-state

Note: Grey shaded region represents the 5th to 95th percentiles of the adult exposure for the patients in the population PK dataset. The horizontal dashed lines represent the 5th and 95th percentiles and the horizontal solid line represents the 50th percentile (median) of the adult exposure for the patients in the population PK dataset. Dots represent individual values.

Figure 20 Simulated Larotrectinib Exposure Grouped by Age

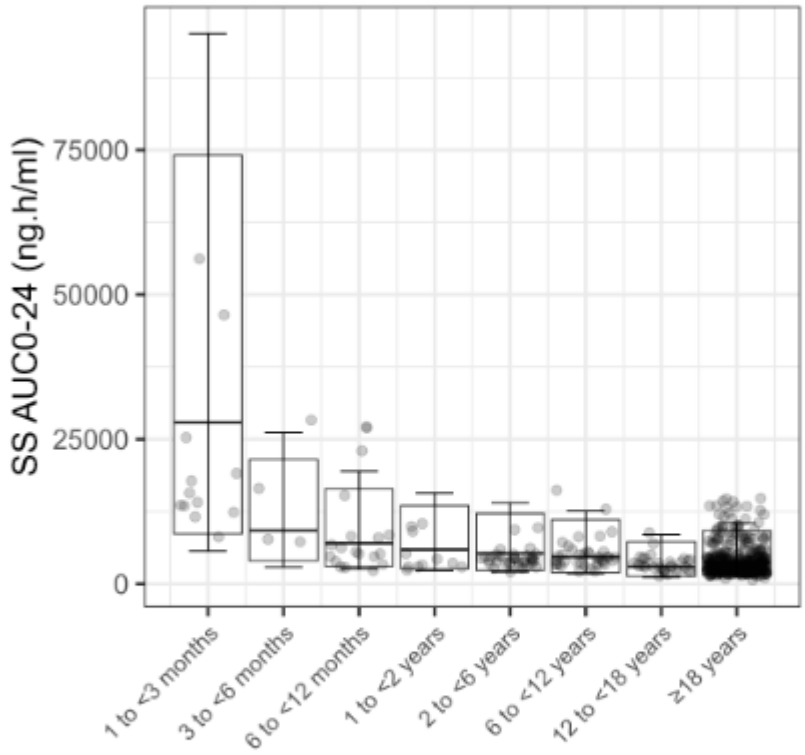


Source: baye-laro-sim-20241216-v1.Rmd
AUC_{0-24}=area under the plasma concentration-time curve from 0 to 24 hours; C_{max}=peak concentration; Ctrough=trough concentration; ln=natural logarithm; SS=steady-state.
Note: Blue shaded regions represent the 95% confidence interval for the 5th and 95th percentiles of the simulated data (90% prediction interval). The black dashed line within the blue shaded region represents the 5th and 95th percentiles of the simulated data. Red shaded region represents the 95% confidence interval for the 50th percentile (median) of the simulated data. The solid black line within the red shaded region represents the 50th percentile (median) of the simulated data. Grey shaded region represents the 5th to 95th percentiles of the adult exposure for the patients in the population PK dataset. The horizontal dashed lines represent the 5th and 95th percentiles and the horizontal solid line represents the 50th percentile (median) of the adult exposure for the patients in the population PK dataset.

Model's predictive capability

The popPK model was used to simulate larotrectinib exposures at the recommended therapeutic dosing regimen for adults and paediatric patients. The simulated exposure levels obtained with the virtual paediatric subjects were generally consistent with the exposure levels obtained for the subjects in the PK dataset using their individual post-hoc parameter estimates, as demonstrated in Figure 10. In particular, for patients <3 months of age, simulations suggest that the recommended therapeutic regimen of 100 mg/m2 up to a maximum of 100 mg may result in 4-fold higher steady state Cmax and 7-to-8-fold higher AUCss than the ones observed in adults. Compared to adult patients, the recommended therapeutic regimen of 100 mg/m2 up to a maximum of 100 mg for paediatric patients between 3 months and 6 years of age results in an approximately 2-fold higher steady state Cmax and a 1-to-3-fold higher AUCss in paediatric patients. Lastly, for paediatric patients older than 6 years of age, the recommended therapeutic regimen gives comparable steady state Cmax and AUCss as observed in adults. These findings are in line with the simulated post-hoc exposures from subjects included in the population PK analysis.

Figure 10: Boxplot of Simulated Larotrectinib SS AUC_{0-24} in Virtual Patients Overlayed with Posthocs SS AUC_{0-24} Grouped by Age



Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from 0 to 24 hours; IQR = interquartile range; PK = pharmacokinetic(s); SS=steady-state
Note: The boxplot displays the median (central line), IQR (box edges), whiskers (smallest and largest values within 1.5×IQR from the quartiles) of the simulated virtual patient population. The black circles represent the exposure for all patients in the population PK dataset. In the 1 to <3 months age category there is one individual with an age of ~18 days for which the posthocs were included.

The results of the simulated exposures using the recommended therapeutic dosing regimen thus indicate that:

- total exposure (median) for paediatric patients was within the 90% PI for adults for all age and body weight groups, except for patients belonging to the youngest (<3 months) and lightest (0 to 10 kg) groups;
- maximum concentrations for paediatric patients ≥6 years of age or ≥15 kg of body weight was similar to adults.

Summary

2.1 Neurodevelopment and cognitive function

The CNS undertakes various developmental milestones during childhood and adolescence. Critical periods of neuroplasticity that occur during this time, along with the concurrent weakness of innate defence systems, result in a developing CNS with unique nuances compared with the fully developed adult brain. Exposure to toxic agents (i.e., chemotherapeutics) during the neurodevelopmental periods in childhood is likely to have uniquely damaging consequences. Cancer therapies (particularly chemotherapy) can induce neuronal apoptosis, neuroinflammation, mitochondrial dysfunction, oxidative stress, DNA damage, and neuro-endocrine imbalance whilst disrupting cortical white matter, blood–brain barrier integrity, and hippocampal neurogenesis (Davies et al. 2024).

Many patients experience changes in cognition as a side effect of both cancer and cancer treatment. This occurs with both CNS tumours and non-CNS tumours and in both children and adults (Hardy et al. 2018). Specific treatments for childhood cancer, especially those that directly impact nervous system structures, may result in sensory, motor, and neurocognitive deficits that may have adverse effects on functional status, educational attainment, and future vocational opportunities (P. D. Q. Paediatric Treatment Editorial Board 2024). Neurologically, 1 in 3 childhood cancer survivors demonstrate a degree of cognitive impairment which persists into adulthood. As many as half of paediatric patients with brain tumours will develop progressive neurocognitive decline. The cognitive impairment includes reduced IQ, deficits in attention and processing speeds, poor short- and long-term memory, and executive dysfunction (i.e., poor self-regulation). Risk factors for cancer-related cognitive impairment in children include genetic factors, female sex, younger age at diagnosis, chemotherapy dose, and both dose and field size for radiation (Hardy et al. 2018).

Starting with Study 20290 protocol version 11.0 (dated 10 JUL 2019), developmental and psychological milestones assessment began to be conducted by performing developmental surveillance at each study/clinic visit according to local standards and by encouraging parents via Investigators to monitor the milestones between visits. Recommendations for Preventive Paediatric Health Care including developmental and psychological milestones assessment from the American Association of Paediatrics were provided to Investigators. Abnormalities identified were captured in either the medical history or adverse event eCRFs as appropriate.

Neurodevelopment including cognitive function was assessed in all patients in Study 20290 using symptom -directed neurological examinations, neurodevelopmental AE analysis, and, in addition, specific for children from 1 month of age up to 66 months (i.e. 5 years and 6 months of age), using the Ages & Stages questionnaire, 3rd edition (ASQ3). Results as of the data cut-off date of 20 JUL 2024 are presented in the following sections.

Data are being assessed at screening for newly enrolled participants and thereafter up to 5 years from the first study treatment. The score of the ASQ3 questionnaire is captured in the database

2.1.1 Neurodevelopment including cognition, symptom-directed neurological examinations, and TEAEs associated with neurodevelopment

2.1.1.1 Neurocognitive development (ASQ3 questionnaire)

The ASQ3 questionnaire, a screening tool to monitor neurocognitive developmental milestones in children between the ages of one month to 5.5 years, was implemented in Study 20290 in APR 2020 (for new patients enrolled under study protocol amendment version 12.0, dated 21 APR 2020). The comprehensive screening questionnaires applicable to the patients' age were collected at age specific time points up from 1 month of age up to 66 months of age (i.e., 5 years and 6 months; including during wait-and-see periods, after resection surgery resulting in negative margins and active safety follow-up). The questionnaire was administered at screening for newly enrolled patients and every 6 months thereafter.

The ASQ3 questionnaire comprises 5 domain areas: communication, gross motor, fine motor, problem solving, and personal-social skills. Each domain area comprises 6 questions, the answers to which are scored and categorized (based on their total score) into an overall domain assessment of "well above", "monitor", or "below".

Since implementation, 21 patients (age range: 2 to 60 months) have had ASQ3 assessments, with 16 patients having 2 or more questionnaires completed.

To date, the Investigator assessment data collected using the ASQ3 questionnaire for the 5 developmental domains indicate that neurocognitive development milestones are not at risk in these patients. Neurodevelopmental milestone assessments from the ASQ3 questionnaires of the youngest patients exposed to larotrectinib treatment continue to be collected and evaluated.

2.1.1.2 Symptom-directed neurological examinations

In addition to the ASQ3 questionnaires in the youngest patients enrolled, for all patients in Study 20290 (N=154; age range: 0.1 to 20.5 years), symptom-directed neurological examinations were performed. Neurological observations by Investigators were reported on the neurological exam page in the eCRF and graded according to CTCAE. Relation to larotrectinib was not recorded for neurological examinations. Neurological observations are subsequently referred to as neurological symptoms.

Overall, 59 patients (38%) in Study 20290 had at least one neurological symptom. Of the 59 patients, the majority (34 patients) had a primary diagnosis of CNS tumours; 21 of the 34 patients with primary CNS tumours were reported with neurological symptoms while on treatment. Overall, 12 patients (8%) had at least one neurological symptom of CTCAE Grade 3. Grade 3 symptoms occurring in ≥2 patients were ataxia in 5 (3%) patients, cognitive disturbance in 4 patients (3%), and neuralgia, 'other' (including dysphagia in one patient and dysarthria and pyramidal tract symptoms in one patient) and paraesthesia in 2 patients (1%) each. No patients had neurological symptoms of Grade 4 or 5, and all other reported events were of Grade ≤2.

2.1.1.3 TEAEs associated with neurodevelopment

The impact of larotrectinib treatment on neurodevelopment (such as attention, comprehension, learning, memory, and speaking) of patients in Study 20290 was also evaluated using the following MedDRA terms: HLGT 'Cognitive and attention disorders and disturbances', HLT 'Developmental motor skills disorders', HLT 'Developmental disorders cognitive', HLT 'Memory loss (excluding dementia)', HLT 'Mental impairment (excluding dementia and memory loss)'. Overall, 10/154 patients (6%) had at least one TEAE associated with neurodevelopment (Table 10). All TEAEs associated with neurodevelopment were of CTCAE Grade ≤2. The most common neurodevelopment-associated TEAE was disturbance of attention in 6 patients (4%). Two patients (1%) had a Grade 1 event of 'memory impairment', which was considered related to larotrectinib treatment by the Investigator; no action was taken with the study drug.

Table 10: TEAEs associated with neurodevelopment by *NTRK* fusion, maximum severity and preferred term in Study 20290 (data cut-off date 20 JUL 2024)

MedDRA Preferred term	Maximum CTCAE grade	*NTRK* Fusion N=146 n (%)	Non-*NTRK* Fusion N=8 n (%)	Total N=154 n (%)
Any	Grade 1	8 (5)	0	8 (5)
	Grade 2	2 (1)	0	2 (1)
	Total	10 (7)	0	10 (6)
Disturbance in attention	Grade 1	6 (4)	0	6 (4)
	Total	6 (4)	0	6 (4)
Memory impairment	Grade 1	4 (3)	0	4 (3)
	Total	4 (3)	0	4 (3)
Attention deficit hyperactivity disorder	Grade 2	2 (1)	0	2 (1)
	Total	2 (1)	0	2 (1)
Cognitive disorder	Grade 1	1 (<1)	0	1 (<1)
	Total	1 (<1)	0	1 (<1)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; HLGT = High Level Group Term; HLT = High Level Term; N = total number of participants (100%); n = number of patients with event/in category; MedDRA = Medical Dictionary for Regulatory Activities; *NTRK* = neurotrophic tyrosine receptor kinase.

Notes: Participants are counted once within each preferred term.

Based on MedDRA, v.27.0, HLGT: cognitive and attention disorders and disturbances, and HLTs: developmental motor skills disorders, developmental disorders cognitive, memory loss [excluding dementia], mental impairment [excluding dementia and memory loss].

Severity grade assignment based on CTCAE (v4.03): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening).

In addition, a pooled analysis of TEAEs associated with neurodevelopment was performed for paediatric patients (<18 years of age) across all 3 clinical studies (20288, 20289, and 20290), using the same search criteria as shown above. There were 122 patients younger than 12 years of age, and 32 patients 12 years of age up to less than 18 years of age for a total of 154 paediatric patients pooled for this assessment. This included 148 patients from Study 20290 and 6 patients from Study 20289.

Overall, 9/154 paediatric patients (5.8%) had at least one TEAE associated with neurodevelopment. All TEAEs associated with neurodevelopment were of CTCAE Grade ≤2, and none of the events were assessed as serious. The most common neurodevelopment associated TEAE was disturbance of attention in 6 patients (3.9%) (5 patients with a Grade 1 event, and 1 patient with a Grade 2 event). Three patients (1.9%) had Grade 1 memory impairment, 2 patients (1.3%) had Grade 2 attention deficit hyperactivity disorder, and 1 patient (0.6%) had Grade 1 cognitive disorder. TEAEs associated with neurodevelopment were considered related to larotrectinib treatment by the Investigator in 2 patients (1.3%): in one patient with Grade 2 disturbance in attention and one patient with Grade 1 memory impairment; no action was taken with the study drug for either event. TEAEs associated with neurodevelopment across all 3 clinical studies are presented by age group in Section 2.1.1.3.1.

2.1.1.3.1 TEAEs associated with neurodevelopment by age group

Duration of larotrectinib treatment by paediatric age group is presented in Table 11 for the pooled data from Studies 20288, 20289, and 20290 as of the database cut-off date of 20 JUL 2024.

Among the paediatric age groups, the longest treatment exposure was in the youngest age group of patients <3 months of age, with the median time of 24.74 (range: 4.8 to 67.7) months on treatment. Study treatment period includes all patients who were receiving active treatment or, for Study 20290 only, were in a protocol-specified drug hold period (i.e., the wait-and-see period).

Table 11: Duration of larotrectinib treatment by pediatric age group (data cut-off date 20 JUL 2024)

	Birth – <3 months N=13	3 – <6 months N=4	6 – <12 months N=19	12 – <24 months N=11	2 – <6 years N=36	6 – <12 years N=39	12 – <18 years N=32
Time on treatment [a], months							
Mean (SD)	28.93 (20.56)	22.58 (19.81)	21.19 (18.76)	30.03 (26.22)	28.54 (23.05)	27.70 (26.80)	20.51 (23.60)
Median	24.74	16.10	14.65	22.51	21.60	20.17	11.56
Range	4.8, 67.7	7.4, 50.7	4.3, 71.3	2.5, 70.4	0.5, 89.1	1.0, 99.4	0.4,84.6
Total number of cycles initiated [b]							
Mean (SD)	31.4 (22.1)	24.5 (21.5)	23.1 (20.1)	32.3 (28.3)	31.0 (24.8)	30.2 (29.1)	22.3 (25.4)
Median	27.0	17.5	16.0	24.0	23.5	22.0	13.0
Range	6, 72	8, 55	5, 76	3, 77	1, 97	1, 109	1, 89

Abbreviations: N = total number of patients (100%); n = number of patients with event/in category; SD = standard deviation
Notes: Percentages are calculated based on the number of patients in the column heading as the denominator.
Time on treatment = (last dose date - first dose date + 1)/30.4375 for patients who permanently discontinued larotrectinib before the visit cut-off. Time on treatment = (last visit date - first dose date + 1)/30.4375 for patients receiving larotrectinib as of the visit cut-off date.
a This category includes all patients who were receiving active treatment or, for Study 20290 only, were in a protocol-specified drug hold period (i.e., the wait-and-see period).
b Planned cycle length was 28 days.

An overview of TEAEs associated with neurodevelopment by paediatric age group is presented in Table 12 for the pooled data from Studies 20288, 20289, and 20290 as of the database cut- off date of 20 JUL 2024. Table 13 presents a summary of the TEAEs associated with neurodevelopment by paediatric age group and MedDRA PT. Of note, due to the small and varying sample sizes in the paediatric age groups, only limited comparisons and conclusions can be made.

Overall, there were 9/154 paediatric patients (5.8%) with at least one TEAE associated with neurodevelopment, 1 patient in the <3 months age group, 1 patient in the 2 to <6 years age group, 4 patients in the 6 to <12 years age group, and 3 patients in the 12 to <18 years age group (Table 12). None of the events reported in paediatric patients were assessed as serious, and all events were Grade ≤2 in severity, and none led to permanent discontinuation or interruption/reduction of larotrectinib treatment (TLFs for PIP03 questions_20 JUL 2024, Tables 1/11 through 1/16).

TEAEs associated with neurodevelopment were considered related to larotrectinib treatment by the Investigator in 2 paediatric patients: in one patient in the 6 to <12 years age group with Grade 1 memory impairment and one patient in the 12 to <18 years age group with Grade 2 disturbance in attention; no action was taken with the study drug for either event.

The only patient in the age group of <3 months (with IFS) reporting a neurodevelopment PT was 0.6 months (18 days) old at the start of the larotrectinib treatment. At the age of 3.2 years, the patient was diagnosed with a PT attention deficit hyperactivity disorder with a worst grade of 2 that was considered not related to larotrectinib and non-serious by the Investigator. The event was ongoing at the time of the data cut-off date of 20 JUL 2024 when the patient had received larotrectinib for 67.7 months (including approximately 1 month of wait-and-see). Please note that this patient achieved radiologic CR by IRC and Investigator and went to wait-and-see period per protocol but had a recurrence about a month later. The patient continues to benefit from ongoing larotrectinib treatment with a sustained BOR of CR by Investigator as of 20 JUL 2024 data cut-off date.

There were no reported neurodevelopment AEs in the remaining 12 patients in the <3 months age group as of the cut-off date of 20 JUL 2024. Even with the higher drug exposure in the youngest patient population, there is no observed trend of a negative impact on efficacy and safety or increased risk in neurodevelopment in the youngest patients over time.

Table 12: Overall summary of TEAEs associated with neurodevelopment by pediatric age group (data cut-off date 20 JUL 2024)

	Patient incidence, n (%)						
	Birth – <3 months N=13	3 – <6 months N=4	6 – <12 months N=19	12 – <24 months N=11	2 – <6 years N=36	6 – <12 years N=39	12 – <18 years N=32
Any TEAE							
All	1 (8)	0 (0)	0 (0)	0 (0)	1 (3)	4 (10)	3 (9)
Related to larotrectinib	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	1 (3)
Grade 3 or 4 TEAE							
All	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Related to larotrectinib	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
TEAE leading to study drug discontinuation							
All	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Related to larotrectinib	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious TEAE							
All	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Related to larotrectinib	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fatal TEAE							
All	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Related to larotrectinib	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; HLGT = High Level Group Term; HLT = High Level Term; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of participants (100%); n = number of patients with event/in category; TEAE = treatment-emergent adverse event

Notes: Percentages are calculated based on the number of patients in the column heading as the denominator.
TEAEs are defined as AEs that start on or after the first administration of larotrectinib.
Related events are those judged by the Investigator as related to larotrectinib.
Based on MedDRA, v.27.0, HLGT: cognitive and attention disorders and disturbances, and HLTs: developmental motor skills disorders, developmental disorders cognitive, memory loss [excluding dementia], mental impairment [excluding dementia and memory loss].
Severity grade assignment based on CTCAE (v4.03): Grade 3 (severe), Grade 4 (life-threatening). Grade 3 or 4 may not be the maximum severity of the events for a specific patient.
Source: TLFs for PIP03 questions_20 JUL 2024, Tables 1/3, 1/4

Table 13: TEAEs associated with neurodevelopment by pediatric age group and Preferred Term (data cut-off date 20 JUL 2024)

	Patient incidence, n (%)						
MedDRA Preferred Term	Birth – <3 months N=13	3 – <6 months N=4	6 – <12 months N=19	12 – <24 months N=11	2 – <6 years N=36	6 – <12 years N=39	12 – <18 years N=32
Any	**1 (8)**	**0**	**0**	**0**	**1 (3)**	**4 (10)**	**3 (9)**
Disturbance in attention	0	0	0	0	1 (3)	2 (5)	3 (9)
Memory impairment	0	0	0	0	0	3 (8)	0
Attention deficit hyperactivity disorder	1 (8)	0	0	0	1 (3)	0	0
Cognitive disorder	0	0	0	0	0	1 (3)	0

Abbreviations: HLGT = High Level Group Term; HLT = High Level Term; N = total number of participants (100%); n = number of patients with event/in category; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

Notes: Percentages are calculated based on the number of patients in the column heading as the denominator.
Participants are counted once within each preferred term.
Based on MedDRA, v.27.0, HLGT: cognitive and attention disorders and disturbances, and HLTs: developmental motor skills disorders, developmental disorders cognitive, memory loss [excluding dementia], mental impairment [excluding dementia and memory loss].
Source: TLFs for PIP03 questions_20 JUL 2024, Tables 1/5, 1/6

Conclusion

Consistent with the previous reported data and current information in the labelling, the youngest patients under the age of 3 months showed greater variability and higher larotrectinib exposures compared to adult patients. However, the analysis of safety data including AEs related to neurodevelopment in patients who started larotrectinib under the age of 3 months, did not indicate any risk to the neurodevelopmental milestones when the same patients grew older. This conclusion is also supported by the information obtained from the symptom-directed neurology examination and the ASQ3 questionnaire in paediatric patients in Study 20290. Therefore, with demonstrated efficacy in all patients under the age of 3 months (3 partial responses and 9 complete responses) and no additional safety concerns, the sponsor recommends maintaining the current dosing regimen of 100 mg/m2 BID. The benefit-risk balance in the <3 months age group is considered to be positive. It is also important to note that further evaluation of the developmental effects of larotrectinib in paediatric patients is ongoing in Study 20290 and will continue until the patients withdraw from the study or the study is closed.

Rapporteur Assessment

The MAH has presented the up-to-date available PK information from children treated with larotrectinib aged **from birth through 21 years** with advanced solid or primary CNS tumours. In total, data from 146 children with NTRK fusion positive tumours, of whom 13 were aged <3 months, and 23 were 3 months to <1 year old.

As a sparse PK sampling schedule was used, AUC derived using observed PK samples is uncertain. The MAH has compared the concentrations at matching time points across the age groups. Comparison of concentrations at individual timepoints confirm a higher exposure in the youngest age group, children <3 months of age.

As PK samplings for most paediatric patients in Study 20289 and Study 20290 are sparse samplings, a population PK approach was also applied to estimate the effect of age on larotrectinib exposure. The population PK model parameters were estimated using 5,768 PK samples from 526 subjects (including healthy volunteers and patients) from these studies. Among paediatric patients, there were 12 patients in the 1 to <3 months age group (including one patient of 18 days), 4 patients in the 3 to <6 months age group, 19 patients in the 6 to <12 months age group, 11 patients in the 1 to <2 years age group, 37 patients in the 2 to <6 years age group, 38 patients in the 6 to <12 years age group, and 32 patients in the 12 to <18 years age group. In addition, intrinsic and extrinsic factors that influence larotrectinib exposure were identified.

The final population PK model was then used to simulate larotrectinib exposures at the recommended therapeutic dosing regimen for adults and paediatric patients. Consistent with what had been reported in previous submission, the youngest age group (<3 months of age) is associated with high exposure compared to adult patients, and older children. In addition to the PK update, the MAH submitted a summary of safety data related to neurodevelopment in the 154 participants in the SCOUT study.

The MAH informed on the ASQ3 questionnaire, which is a screening tool to monitor neurocognitive developmental milestones in children aged 1 month – 5.5 years and was implemented for patients enrolled from April 2020 and onwards (protocol version 12.0). So far, 21 patients have had ASQ3 assessments and according to the MAH there are no indications that neurocognitive development milestones are at risk.

Furthermore, submitted data from symptom-directed neurological examinations reveal that 21 (13.6%) of the patients reported neurological symptoms of any grade. All these patients, though, had primary CNS tumours. Most neurological symptoms (92%) were grade $\leq$2 and 12% were grade 3. Cognitive disturbances were reported in five (3%) of the patients. This was in line with a total of 9/154 (5.8%) patients reporting TEAEs associated with neurodevelopment, of which the most common was PT `Disturbance in attention´ (n=6 [4%]). All neurodevelopment TEAEs were grade $\leq$2. These nine TEAEs were reported in 1/13 (8%) children aged from birth to <3 months, 1/36 (3%) children aged 2 - <6 years, 4/39 (10%) children aged 6 - <12 years, and 3/32 (9%) children aged 12 - <18 years. One TEAE (disturbance in attention) in a child 12 - <18 years of age was assessed as related to larotrectinib.

Conclusion

The posology in children is based on a PK bridge. Available data now confirm that the exposure in children aged <3 months is significantly higher than in older children. Although safety data do not indicate any obvious differences across age groups, the limited number of patients in each age group and the inherent developmental aspects associated with different ages makes it difficult to thoroughly assess and interpret safety differences across ages. Moreover, the target NTRK is understood to be involved in neurodevelopment, Thus, safety data may aid but not decide on an adequate dose in children. Thus, an updated PK modelled recommended dose in children aged 1-3 months is requested. This should be submitted in a separate variation application.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: VTRAKVI® Active substance:

Study title	Study number	Date of completion	Date of submission of final study report
A Twice Daily (12 hours apart) Oral (Gavage) Dose Range-Finding Toxicity Study of LOXO-101 in Juvenile Rats	LOXO-101-TOX-020	Report Approval: 23 Aug 2017	24 Aug 2018
A Twice Daily (12 hours apart) Oral (Gavage) Dose Range-Finding Toxicity Study of LOXO-101 in Juvenile Rats	LOXO-101-TOX-022	Report Approval: 29 Sep 2017	24 Aug 2018
A Twice Daily (12 hours apart) Oral (Gavage) Toxicity Study of LOXO-101 in Juvenile Rats with Recovery	LOXO-101-TOX-021	Report Approval: 10 Jan 2018	24 Aug 2018

Clinical studies

Product Name: VTRAKVI® Active substance: Larotrectinib

Study title	Study number	Date of completion	Date of submission of final study report
A Phase 1/2 Study of the Oral TRK Inhibitor Larotrectinib in Pediatric Patients with Advanced Solid or Primary Central Nervous System Tumors	20290	Cut-off dates: Efficacy (N=38), 20 JUL 2023; Safety (N=40) 18 MAY 2024, PK (N=14) 10 JAN 2024, Biomarkers (N=38), 20 JUL 2023; Palatability / new oral solution (N=17) 18 MAY 2024	13 Nov 2024
A Comparison of Clinical Outcomes in *Neurotrophic Tyrosine Receptor Kinase* (*NTRK*) Fusion-Positive Primary Central Nervous System (CNS) Patients Treated in Larotrectinib Study SCOUT with Historical Data from Existing Databases	NA	Report Approval: 04 Oct 2024	13 Nov 2024