Amsterdam, Jan 26th 2023
EMA/CHMP/26478/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

VITRAKVI

larotrectinib

Procedure no: EMEA/H/C/004919/P46/008

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[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	28 Nov 2022	28 Nov 2022	☐
☐	CHMP Rapporteur Assessment Report	03 Jan 2023	03 Jan 2023	☐
☐	CHMP members comments	16 Jan 2023	16 Jan 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	19 Jan 2023	N/A	☐
☒	CHMP adoption of conclusions:	26 Jan 2023	26 Jan 2023	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

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1. Introduction

On 26th October 2022, the MAH submitted a completed paediatric study for larotrectinib (Vitrakvi), in accordance with Article 46 of Regulation (EC) No1901/2006.

These data are also submitted as part of a post-authorisation measure.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the PIP02 report was prepared in accordance with the approved Pediatric Investigational Plan (EMEA-001971-PIP02-16-M04, decision date 03 DEC 2021).

According to the MAH, this is the last report listed in the program (of PIP02). A line listing of all the concerned studies is annexed.

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 PIP02 report evaluated treatment of pediatric patients from birth to less than 18 years of age with advanced solid tumors harboring an NTRK fusion, of all conditions included in the category of malignant neoplasms (except CNS tumors, hematopoietic and lymphoid neoplasms).

The main components of the PIP02 report were the efficacy, safety, pharmacokinetics (PK) and biomarker results in the PIP02 population based on Study 20290 (SCOUT) (N=105). Additional efficacy and safety results for a subset of patients who received the new age-appropriate oral solution (N=14) in Study 20290 (SCOUT), and palatability of the new age-appropriate oral solution were also described. Information on the new age-appropriate oral solution and an assessment of administration of this age-appropriate oral solution via nasogastric tube were also provided.

Sensitivity analyses for efficacy were presented for the pooled group of pediatric and adult patients across Studies 20288, 20289, and 20290 (N=244).

The individual studies included in the PIP02 report:

- Development of larotrectinib solution 2% 50 mL for oral use: The development of the new age-appropriate larotrectinib solution 2 % 50 mL for oral use
- NGT Study S21001492: Extractables study for nasogastric tubes
- Study 20290 (SCOUT): The main analysis of efficacy, safety, PK and biomarkers in the PIP02 report is based on data from a subset of patients in Study 20290.
- Study 20288, Study 20289, and Study 20290 data: A sensitivity analysis of efficacy of pediatric and adult patients is based on pooled data from these 3 studies.
- Study 21767: A historical analysis evaluating results from Study 20290 and data from Institute Curie and CWS registries.

2.3.2. Clinical study

20290, SCOUT

Hereafter referred to as Study 20290.

Description

Study 20290 is an ongoing multicenter open-label Phase 1/2 study in pediatric patients aged from birth to 21 years with advanced solid or primary CNS tumors. The study is divided into a Phase 1 dose escalation portion, a Phase 1 dose expansion portion, and a Phase 2 portion.

Methods

The primary study objectives of the Phase 1 portion (dose escalation and dose expansion) include the characterization of safety and DLT, PK, identification of the MTD or appropriate dose of larotrectinib for further study, description of antitumor activity (ORR and other efficacy parameters), and pain and health-related QoL.

In the Phase 2 portion, enrollment is restricted to patients with tropomyosin receptor kinase (TRK) fusion cancer with measurable disease.

The primary study objective of the Phase 2 portion is to determine the ORR as determined by an independent radiology review committee following treatment with larotrectinib in pediatric patients with an advanced cancer harboring a gene fusion involving NTRK1, NTRK2, or NTRK3 (collectively referred to as NTRK gene fusions) fusions. A Safety Review Committee (SRC) oversaw the safety aspects of the study and rendered dose escalation decisions in the Phase 1 portion of the study through ongoing review of serious AEs and other safety trends throughout the conduct of the study. The membership of the SRC consisted of the Sponsor's representatives and clinically qualified individuals from each active clinical site.

The study is ongoing and will continue beyond the above specified dataset for PIP02; the MAH states that such continuation is not considered to be part of the PIP02.

Sample size

N/A

Randomisation and blinding (masking)

The study was not randomized nor blinded.

Statistical Methods

Efficacy results are based on independent review committee (IRC) assessments. The performed evaluations were exploratory.

Results

The latest results of the study as of the data cut-off date of 20 JUL 2021 are presented in detail in the fourth interim analysis in Report PH-42037, dated 21 JAN 2022.

Study 20290 was conducted worldwide in a predominantly NTRK positive population, without ethnic

specifications. As of 20 JUL 2021, 135 patients in total had been treated in the study. Enrollment in the Phase 1 dose escalation (N=24) and the Phase 1 expansion (N=16) was completed, and enrollment for the Phase 2 portion was still ongoing (N=95).

- A total of 126 patients (93%) had an NTRK gene fusion. The median age across all dose groups was 4.9 years (range <1 month to 20.5 years). Overall enrollment was balanced by gender, and the most commonly represented race was white, followed by Asian.
- A confirmed ORR of 71% (95% CI: [62, 79]) and clinical benefit rate of 93% (95% CI: [87, 97]) was obtained in the 115 evaluable NTRK gene fusion patients, based on investigator assessments. Patients with TRK fusion cancers treated with larotrectinib exhibited responses across NTRK isoforms, tumor types and patient ages.
- At a median follow-up time of 25.8 months, 26 of the responding patients had progressed. The median DOR had not been reached. The DOR was >6 months for 75% and was >12 months for 63% of responder patients with TRK fusion cancer.
- The median time to response of confirmed CR or PR was 57 days (range: 27, 276).
- The safety profile of larotrectinib was based on 135 dosed patients (126 patients with NTRK gene fusions). The patients were between less than 1 month and 20.5 years of age and had received study treatment for up to 63.5 months, at starting doses ranging from 17.5 to 120.1 mg/m2 BID. An MTD was not reached.
- Treatment-emergent adverse events (TEAEs) commonly consisted of gastrointestinal symptoms (nausea, vomiting, diarrhea, and constipation), pyrexia, upper respiratory tract infection, cough, headache, and nasopharyngitis, or related to investigations, i.e., ALT and AST increases, anemia, and neutrophil count decreased. In general, these TEAEs did not interfere with the successful delivery of larotrectinib at the intended dose and schedule.
- Three patients died on study due to an AE unrelated to study treatment, or disease progression and its complications.
- Selected TEAEs of special interest included AST/ALT increases, neurologic events, and neutropenia:
    - Thirty-one patients experienced Grade 2 and/or Grade 3 ALT/AST increase in laboratory values. For 6 patients, dose modification was required; one of these patients had an AE of Grade 3 ALT elevation (DLT) that contributed to study drug discontinuation.
    - In the MAHs evaluation, clinical data indicated an overall mild effect of larotrectinib on CNS, resulting in neurologic events, and most reactions resolved under continued larotrectinib treatment, in the vast majority without any dose reduction. There was one Grade 5 neurologic event of cerebellar hemorrhage that was considered not related to treatment with larotrectinib. One Grade 3 neurologic event (preferred term: irritability) was considered related to larotrectinib.
    - TEAEs due to neutrophil count decreased were noted in 39 (29%) patients across dose cohorts. Of these, Grade 3 TEAEs were reported in 22 patients and Grade 4 TEAEs in 4 patients. Of the 26 patients with Grade 3 or 4 neutropenia, 17 patients had a dose interruption and dose reduction, 3 patients discontinued study drug, and for 6 patients the TEAE resolved without dose modification. Most patients with neutrophil count decreases had returned to their baseline grade or better by the time of the last post-

baseline measurement. It is possible that this was associated with viral infections and the pre-study treatment regimens that are more common in pediatric populations.

In summary, the interim results showed that larotrectinib demonstrated antitumor activity in pediatric patients with locally advanced or metastatic solid tumors with NTRK gene fusions that had little or no effective treatment alternatives. Larotrectinib had a safety profile characterized by recognizable toxicities which were mostly Grade 1 and 2 and were reversible, predictable, manageable, and could be monitored.

2.3.3. PIP02 Study

Description

To meet the reporting requirements of EMEA-001971-PIP02-16-M04, the patients presented in the main analyses in the PIP02 report are a subset of the patients presented in the Clinical Study Report for Study 20290. This subset of patients is referred to throughout the document as the "PIP02 population" and is described below.

Methods

PIP02 population characteristics

A total of 105 patients from Study 20290 were included in the analyses presented in the PIP02 report (i.e., PIP02 population). Patients included were from the Phase 1 part of the study who had received 1 or more doses of larotrectinib, had documented NTRK gene fusion, and were <18 years of age. Patients who enrolled into the Phase 2 part were included if additionally they had a non-primary CNS solid tumor, were treated at a larotrectinib dose of 100 mg/m2 twice daily (BID), and had measurable disease at baseline. (Note: patients with primary CNS tumors from the Phase 1 dose expansion were included in the analysis to fulfil requirements related to sample size.)

The study is ongoing and will continue beyond the above specified dataset for PIP02; the MAH states that such continuation is not considered to be part of the PIP02.

Patients in Study 20290 receiving the new age-appropriate oral solution

The subset of patients from Study 20290 presented in this PIP02 report who received the new oral solution were enrolled in the Phase 2 part of the study and were in Cohort 3 (larotrectinib dose of 100 mg/m2 BID). These patients started their first treatment and continued on treatment using the new oral solution.

The Palatability analysis set is used for the assessment safety and efficacy of the new oral solution in the PIP02 report. Patients who met the following criteria were included:

- Enrolled into phase 2 of Study 20290
- Started first treatment on the new oral solution and used it continually
- Were recruited up to 12 months before the data cut-off 08 APR 2022 (i.e., all patients should have had 12 or even more months of follow-up)
- Therefore, patients with primary CNS cancer and/or no measurable disease at baseline were also eligible to be included in this analysis set.

Treatments

Patients in the Phase 1 dose expansion and all patients in the Phase 2 part received the recommended dose for pediatric patients, i.e., 100 mg/m2 BID (with a maximum of 100 mg BID).

The larotrectinib doses administered were grouped in dose cohorts for Study 20290:
- Dose level 1 (Cohort 1) refers to the 9.6-55 mg/m2 BID cohort
- Dose level 2 (Cohort 2) refers to the 17.3-120 mg/m2 BID cohort
- Dose level 3 (Cohort 3) refers to the 100 mg/m2 BID cohort

Patients in Study 20290 receiving the new age-appropriate oral solution

Oral dosing was based on adult equivalent of 100 or 150 mg BID, then 100 mg/m2 BID (with a maximum of 100 mg BID). Actual doses administered ranged from 17.5 to 120.1 mg/m2 BID Capsules (25 mg and 100 mg) or oral solution (20 mg/mL) New oral solution: 20 mg/mL oral solution; 100 mg/m2 BID.

Outcomes/endpoints

Phase 1: Primary: Safety, DLT; Secondary: DOR, quality of life, safety

Phase 2: Primary: ORR; Secondary: DOR, DCR, PFS, OS, safety, concordance between NTRK profiling, postoperative staging

PIP02 report content and data cut-off (dco) dates:

Efficacy (N=98) and Safety (N=105), PK (N=14), Biomarkers (N=38), dco: 20 JUL 2021;

Palatability / new oral solution (N=14), dco: 08 APR 2022

Table 1. Endpoints for the PIP report

	Study 20290		
	Phase 1	**Phase 2**	**Phase 1 and Phase 2**
Primary endpoints	DLT assessed at each treatment cycle [a], safety assessments	ORR assessed every 2 treatment cycles [d]	
Secondary endpoints	PK parameters [b], MTD [c], ORR		CR, PR, disease progression, DOR, PFS, OS *Biomarkers* [e]: assessment of *NTRK1*, *NTRK2*, and *NTRK3* gene fusion and mutation using ctDNA and archived or fresh tumor samples (as available)
Exploratory endpoints		Palatability assessment, safety and tolerability assessments	HRQoL using PedsQL, functional performance status, pain (FACES), neurocognitive assessment
	Sensitivity analysis		**Study 21767**
Further endpoints	ORR, DOR, PFS, and OS by tumor type, integrating adult and pediatric data across studies 20288, 20289, 20290		Comparison with historical data from Institut Curie "registry" (time-to-event and ORR endpoints)

CR = complete response; ctDNA = circulating tumor deoxyribonucleic acid; DLT = dose-limiting toxicity; DOR = duration of response; HRQoL = health-related quality of life; IRC = independent review committee; MTD = maximum tolerated dose; *NTRK* = neurotrophic tyrosine receptor kinase; ORR = overall response rate; OS = overall survival; PedsQL = Pediatric Quality of Life, PFS = progression-free survival; PK = pharmacokinetics; PIP = pediatric investigational plan; PR = partial response; SAF = safety analysis set

Efficacy endpoints were assessed by IRC.

Note: Phase 1 and Phase 2 are also referred to as Part 1 and Part 2.

[a] No patients in the SAF in Study 20290 for this PIP02 report had a DLT.

[b] PK parameters are described in Table 6-1.

[c] The MTD was not reached in Study 20290.

[d] Assessments were every 2 cycles until Cycle 13, then every 3 cycles.

[e] For patients who progressed or permanently ended treatment (Section 7).

2.3.4. Efficacy results, PIP02 population

Baseline data

A total of 105 patients from Study 20290 were included in the analyses presented in the PIP02 report (i.e., PIP02 population).

The median age of the 105 treated patients across all dose groups in the PIP02 population was 3.33 years, ranging from less than 1 month to 17.8 years. The patient population was generally balanced by gender. Study 20290 is being conducted worldwide in North America, Europe and Asia Pacific. The most commonly represented race was white (61.9%), followed by Asian (17.1%). As the population of patients with an NTRK gene fusion is rare, the ratio between patients of certain ethnicity and/or race could not be influenced.

Among patients receiving the new oral solution, the median age was 2.04 years (range 0.1 to 15.8 years), and the group was also balanced by gender. Patients were predominantly Asian (57.1% of patients), followed by white (35.7%).

Patients in the PIP02 population had locally advanced (59.0%) or metastatic disease (30.5%) or were primary CNS patients (10.5%) at the time of enrollment. The most common malignancies were IFS (46.7%), STS (35.2%), and primary CNS tumors (10.5%). Performance status (Karnofsky or Lansky depending upon age) was high, with a median across all patients of 100.00 (range: 50.00 to 100.00). Overall, 69.5% of the patients had received previous systemic anti-cancer therapy.

Similarly, most patients receiving the new oral solution had locally advanced (64.3%) disease at the time of enrollment The most common malignancies were IFS (50.0% of patients), primary CNS tumors (28.6%), and STS (21.4%). Performance status (based on Lansky or Karnofsky performance status

scales) was also high, with a median of 90.00 (range: 50.0 to 100.0). Overall, 57.1% of the patients receiving the new oral solution had received previous systemic anti-cancer therapy.

Of the 105 patients in the PIP02 safety analysis set (SAF), 98 patients were included in the efficacy evaluation i.e., in the PIP02 EAS. Primary diagnosis was IFS for 47 patients, STS for 34 patients, primary CNS for 11 patients, thyroid cancer for 3 patients, congenital mesoblastic nephroma (CMN) for 2 patients, and melanoma for 1 patient.

Of the 14 patients receiving the new oral solution, 12 were evaluated for efficacy of the new oral solution and were included in the palatability analysis set. Of note, the new oral solution was first administered in FEB 2020 in Study 20290, resulting in relatively short follow-up times for these patients compared with the PIP02 EAS population.

Patients who completed a palatability questionnaire on C1D1 and C1D8 did not need to have a follow-up time of at least 12 months to be included in the analysis of palatability of the new oral solution.

Efficacy Results

Overall response rate

Tumor response was evaluated using RECIST 1.1 for solid tumors (excluding primary CNS tumors) and RANO for primary CNS cancers.

The ORR based on 89 evaluable patients was 84.3% (95% CI: [75.0, 91.1]) in the PIP02 EAS.

For the 12 efficacy evaluable patients in the palatability analysis set, the confirmed ORR was 66.7% (95% CI: [34.9, 90.1]).

ORR by primary diagnosis or by NTRK gene fusion isoform for the PIP02 EAS is presented in table 3. As reflected in the ORR, responses were high in patients with IFS (95.5%, 95% CI: [84.5, 99.4]) and STS (82.4%, 95% CI: [65.5, 93.2]), the most common tumors in the PIP02 EAS population. The sample sizes of the other tumors were insufficient for any generalizations to be made.

Patients with TRK fusion cancers treated with larotrectinib exhibited responses across NTRK isoforms.

Table 2. Best overall response and overall response rate (IRC) (PIP02 EAS, palatability analysis set)

	Total (PIP02 EAS) N = 98	New oral solution N = 12
Best Overall Response, n (%)		
CR [a]	26 (26.5)	2 (16.7)
PR [a]	39 (39.8)	6 (50.0)
Pathological CR (pCR)	10 (10.2)	0
SD	13 (13.3)	1 (8.3)
Progressive disease	4 (4.1)	1 (8.3)
Not evaluable	1 (1.0)	0
Missing	5 (5.1)	2 (16.7)
ORR [b]		
Number of evaluable patients	89	12 (100.0)
ORR (CR + PR + pCR), n (%)	75 (84.3)	8 (66.7)
95% CI [c]	75.0, 91.1	34.9, 90.1

BOR = best overall response; CI = confidence interval; CR = complete response; EAS = efficacy analysis set; IRC = independent review committee; 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; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SD = stable disease

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

[a] CR and PR must have been verified by scan no less than 28 days after the criteria for response were first met.

[b] ORR was defined as the percentage of patients with a BOR of confirmed CR or PR or pCR by RECIST 1.1 (for solid tumors, excluding primary CNS tumors) or RANO (for primary CNS cancers). Excludes patients without measurable disease at baseline and patients continuing treatment without any postbaseline assessment.

[c] 95% CI was calculated by exact binomial calculation.

Source: Module 5.3.5.3, PIP02 report, Table 14.2.2.1/1 and Table 14.3.2.1/1

Table 3. Overall response rate by primary diagnosis or by NTRK fusion isoform (IRC) – confirmed responses (PIP02 EAS with measurable disease at baseline)

Tumor type	**n**	**CR + PR + pCR**	**ORR [95% CI] [a]**
Overall	**89**	**75**	**84.3% [75.0, 91.1]**
IFS	44	42	95.5% [84.5, 99.4]
STS	34	28	82.4% [65.5, 93.2]
Primary CNS	8	3	37.5% [8.5, 75.5]
CMN	2	2	100.0% [15.8, 100.0]
Melanoma	1	0	0% [0.0, 97.5]
***NTRK* gene fusion type**	**N**	**CR + PR + pCR**	**ORR [95% CI] [a]**
Overall	89	75	**84.3% [75.0, 91.1]**
NTRK1	33	27	81.8% [64.5, 93.0]
NTRK2	9	5	55.6% [21.1, 86.3]
NTRK3	37	33	89.2% [74.6, 97.0]
Inferred NTRK3	10	10	100.0% [69.2, 100.0]

CI = confidence interval; CMN = congenital mesoblastic nephroma; CNS = central nervous system; CR = complete response; EAS = efficacy analysis set; IFS = infantile fibrosarcoma; IRC = independent review committee; n = number of evaluable patients (100%); *NTRK* = neurotrophic tyrosine receptor kinase; ORR = overall response rate; pCR = pathological complete response, previously referred to as surgical complete response; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; STS = soft tissue sarcoma

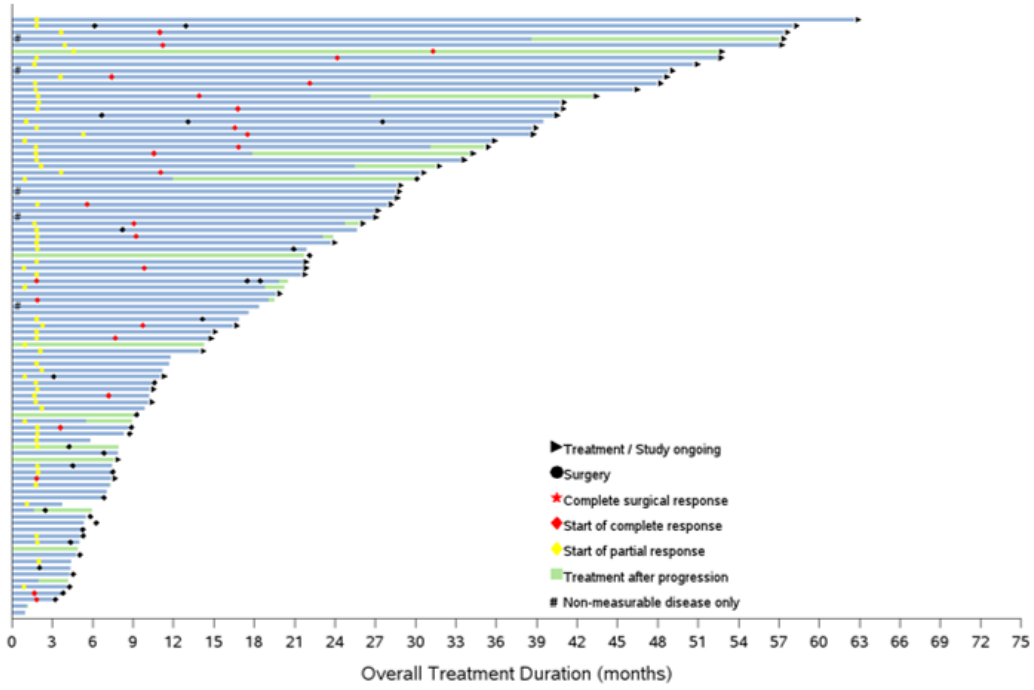
ORR was defined as the percentage of patients with a BOR of confirmed CR or PR or pCR by RECIST 1.1. (for solid tumors, excluding primary CNS tumors) or RANO (for primary CNS cancers)

[a] 95% CI was calculated by exact binomial calculation.

Source: Module 5.3.5.3, PIP02 report, Table 14.2.2.1/2 and Table 14.2.2.1/3

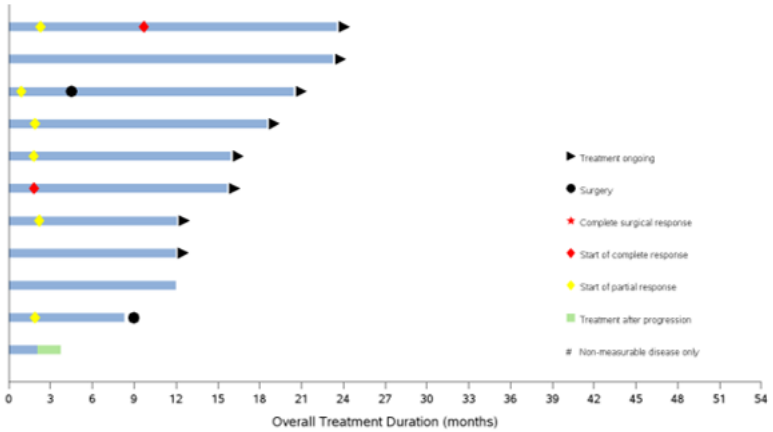
Time to response and overall treatment duration are shown in swimmer plots for the PIP02 EAS and the palatability analysis set, respectively). Most responses were evident within the first 6 months, and many patients were progression-free at their most recent observation.

Figure 1. Swimmer plot of time to response and overall treatment duration (IRC) (PIP02 EAS)



EAS = efficacy analysis set; IRC = independent review committee
Disease assessments based on IRC Assessment. Only time on treatment is displayed.
Includes patients who have a response by IRC available (N=94).
Source: Module 5.3.5.3, PIP02 report, Figure 14.2.2.4/1

Figure 2. Swimmer plot of time to response and overall treatment duration of patients receiving the new oral solution (IRC) (palatability analysis set)



IRC = independent review committee
Includes patients who have a response by IRC available (N=11).
Source: Module 5.3.5.3, PIP02 report, Figure 14.3.2/1

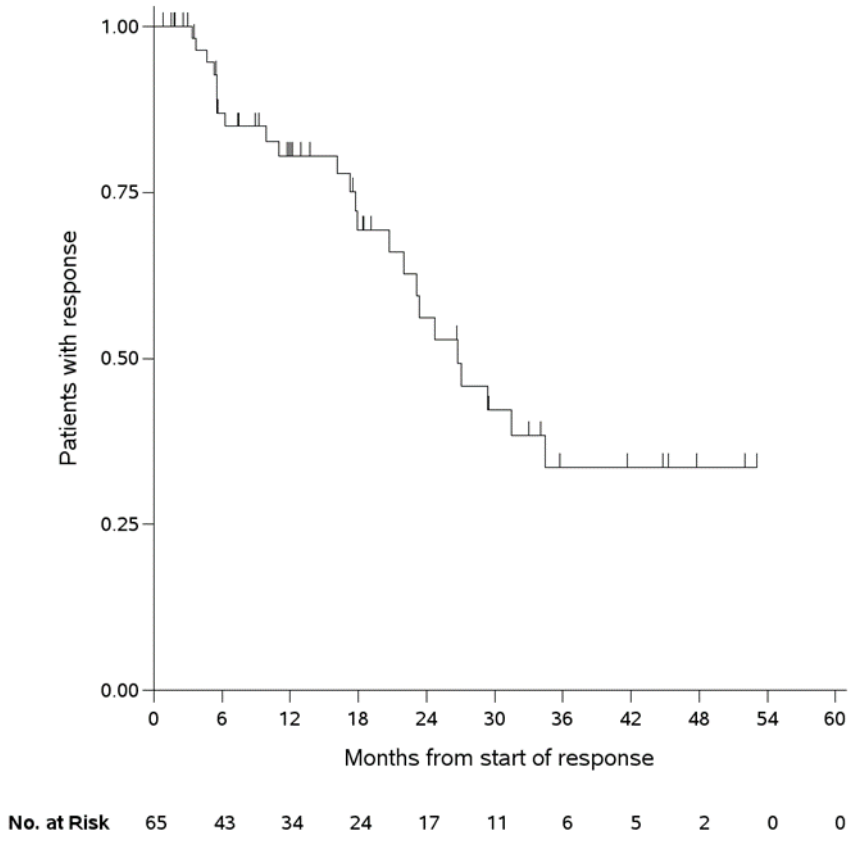
Duration of response

There were 75 responding patients in the PIP02 EAS and 8 responding patients who received the new oral solution. Most responses were continuing at the time of the data cut-off.

For the PIP02 EAS, at the time of the data cut-off, and with a median duration of follow-up of 19.1 months, the median duration of response was 31.4 months (range of 0.0 to 53.0 months). The corresponding Kaplan-Meier curve is presented in Figure 3.

With a median duration of follow-up of 12.0 months, the median DOR was not estimable for patients in the palatability analysis set (range 3.0 to 21.1 months).

Figure 3. Kaplan-Meier plot of duration of response (IRC) (PIP EAS)

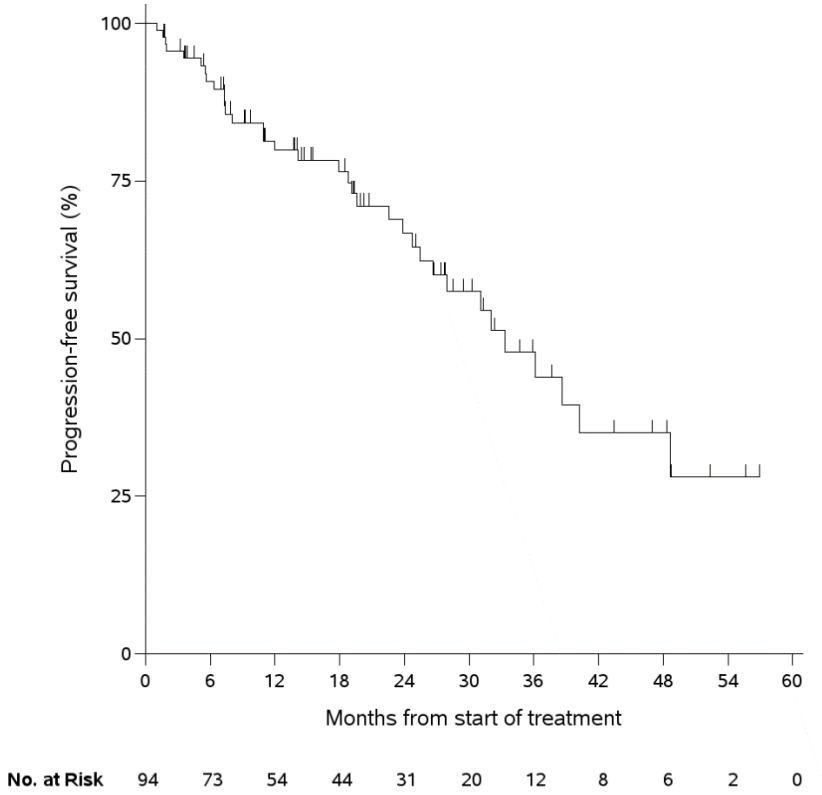


Progression-free survival

In the PIP02 EAS, 94 patients (95.9%) were evaluated for progression by IRC. There were 34 patients (34.7%) with documented disease progression. At the time of the interim data cut-off, the median duration of follow-up for PFS was 20.7 months. The median PFS was 33.3 months, with minimum and maximum PFS ranging from 0.0 to 56.9 months. Based on the Kaplan-Meier method, the rate of PFS for at least 6 months of treatment was 91% (95% CI: [85, 97]), for at least 12 months was 80% (95% CI: [71, 89]), and for at least 48 months was 35% (95% CI: [19, 52]). The corresponding Kaplan-Meier curve for PFS is presented in Figure 4.

For the patients in the palatability analysis set, the median duration of follow-up was 13.8 months. As the new oral solution was introduced in 2020, the median duration of follow-up was shorter than in the PIP02 EAS. There were 4 patients (33.3%) with a PFS event, and the median PFS was not evaluable (range from 2.1 to 23.3 months). The Kaplan-Meier estimated rate of PFS for at least 6 months of treatment was 81% (95% CI: [57, 100]).

Figure 4. Kaplan-Meier plot of progression-free survival (IRC) (PIP EAS)

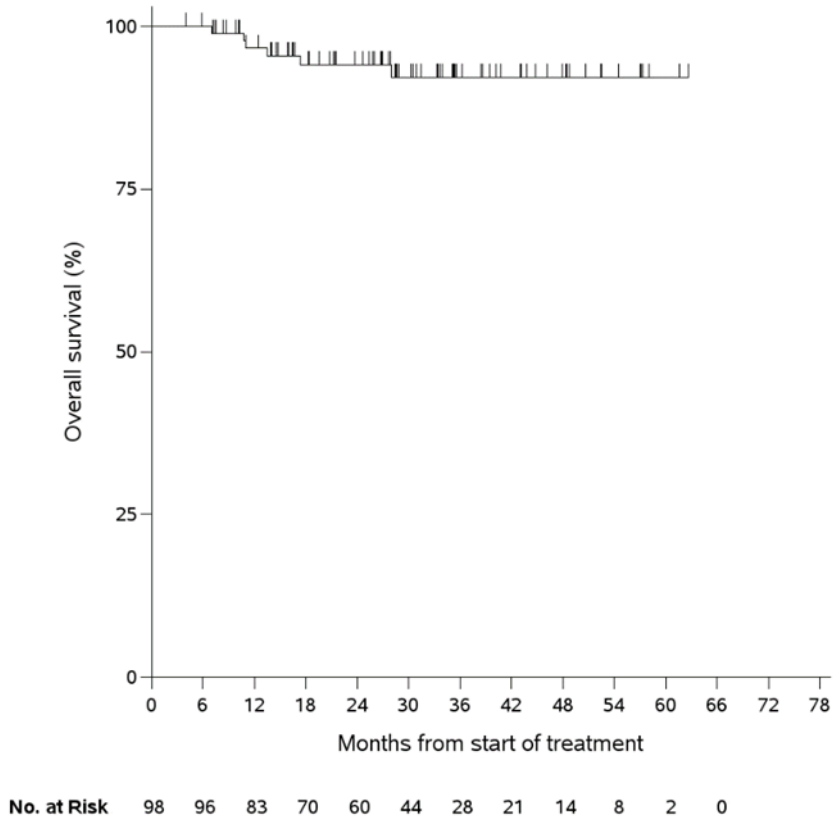


Overall survival

In the PIP02 EAS, 6 of the 98 patients (6.1%) died on or before the cut-off date and the median OS was not reached. The Kaplan-Meier estimate of OS of at least 12 months was 97% (95% CI: [93, 100]). The corresponding Kaplan-Meier curve is presented in Figure 5.

One of the 12 patients (8.3%) in the palatability analysis set died on or before the cut-off date and the median OS was not reached.

Figure 5. Kaplan-Meier plot of overall survival (PIP EAS)



Palatability of the new oral solution

In Study 20290, 7 patients who were treated with the new oral solution completed the palatability questionnaire during Cycle 1, on Day 1 and Day 8 of treatment. The questionnaire was used for evaluation of the appearance, smell, taste, feeling in mouth/texture, and after taste of the new oral solution (possible ratings: very bad, bad, neutral, good, very good, not assessable) and whether it was difficult to swallow.

The overall assessment at both time points (Cycle 1, Day 1 and Day 8) varied among patients, with neutral reported in 3 patients (42.9%), and very good, good, and very bad reported in 2 patients (28.6%) each. The overall assessment was not assessable for 1 patient at Cycle 1 Day 1. Ratings of appearance, smell, taste, feeling in mouth/texture, and after taste also varied among patients. For nearly all patients (6 patients, 85.7%), the new oral solution was not difficult to swallow.

2.3.5. Pooled analysis in pediatric and adult patients: Efficacy results from patients in Studies 20290, 20289, and 20288

For the sensitivity analysis of efficacy (by IRC), a total of 244 adult and pediatric patients were pooled from Studies 20290, 20289, and 20288 and included those who had received 1 or more doses of larotrectinib, had documented NTRK gene fusion, had a non-primary CNS solid tumor with 1 or more measurable lesions at baseline and had begun treatment up to 6 months before the data cut-off 20 JUL 2021 (all patients had at least 5 months of follow-up).

These 244 patients constituted the extended primary analysis set 6 (ePAS6).

- As of 20 JUL 2021, the ORR as assessed by IRC was 69% with an estimated median duration of response of 38.44 months. The response rate observed across patients with different tumor

types supports the use of larotrectinib in a histology-independent (i.e., tumor agnostic) population.

- Adult and pediatric patients with TRK fusion cancers treated with larotrectinib exhibited responses across NTRK isoforms, tumor types and patient ages Overall, there were no major differences between the efficacy results of the pediatric patients from Study 20290 and the pooled adult and pediatric populations of Studies 20290, 20289, and 20288 of the ePAS6. The MAH also found the safety profile of larotrectinib comparable between the two analysis populations.

Additionally, the results from the PIP02 efficacy population (patients <18 years of age, predominantly with IFS or STS) and the adult subgroup of patients in the ePAS6 (≥18 years of age) showed high overall response rates in both groups (84.3% for pediatric patients, 60% for adult patients).

2.3.6. Safety results, PIP02 population

Analysis sets for safety evaluation

The Safety analysis set (SAF) is the main analysis set used for the safety evaluation in the PIP02 report. It includes patients from Phase 1 and Phase 2 parts of Study 20290. Patients who enrolled into the Phase 1 dose escalation or extension cohort of Study 20290 were included in the PIP02 SAF if they fulfilled the following criteria:

- Received 1 or more doses of larotrectinib
- Had documented NTRK gene fusion as determined by local testing
- <18 years of age

Patients who enrolled into Phase 2 of Study 20290 were included in the PIP02 SAF if they fulfilled the following criteria:

- Received 1 or more doses of larotrectinib
- Had documented NTRK gene fusion as determined by local testing
- <18 years of age
- Had a non-primary CNS solid tumor
- Were treated with larotrectinib at dose level 3 (100 mg/m2 BID)
- Had measurable disease at baseline as assessed by the investigator and RECIST 1.1

The Palatability analysis set is used for the assessment safety of the new oral solution in the PIP02 report.

Extent of exposure

In the PIP02 SAF, a median of 16.0 cycles (of 28 days) of treatment had been initiated, with a median study treatment duration of 14.80 months (range: 1.0, 63.5). Median durations were longer in the earlier cohorts, reflecting the earlier initiation of these cohorts and the interim nature of the analysis.

For patients receiving the new oral solution (palatability analysis set), a median of 13.5 cycles had been initiated, with a median study treatment duration of 13.35 months (range: 3.6, 27.0). The

relatively short duration of treatment is largely due to the late initiation of the new oral solution (first patients treated with the new oral solution in FEB 2020).

Summary of adverse events

In the PIP02 SAF, TEAEs were most commonly seen (i.e., in >50% of patients overall) in the Gastrointestinal disorders (81.9%), Infections and infestations (81.0%), General disorders and administration site conditions (68.6%), Investigations (67.6%), Skin and subcutaneous tissue disorders (58.1%), Blood and lymphatic system disorders (58.1%), and Respiratory, thoracic and mediastinal disorders (54.3%).

The most commonly reported TEAEs (occurring in >20% of patients) were vomiting, pyrexia, AST increased, cough, ALT increased, diarrhea, upper respiratory tract infection, neutrophil count decreased, anemia, constipation, nasopharyngitis, headache, and nausea (Table 4). TEAEs that were considered related to larotrectinib occurring in >15% of patients were AST increased, ALT increased, neutrophil count decreased, and anemia.

Table 4. Treatment-emergent adverse events (with overall incidence of more than 20% of patients in either analysis set) (PIP02 SAF and palatability analysis set)

	Patient incidence, n (%)				
Preferred term	Cohort 1 N = 3	Cohort 2 N = 7	Cohort 3 N = 95	Total PIP02 SAF N = 105	New oral solution N = 12
Any TEAE	**3 (100.0)**	**7 (100.0)**	**93 (97.9)**	**103 (98.1)**	**12 (100.0)**
Vomiting	2 (66.7)	6 (85.7)	48 (50.5)	56 (53.3)	3 (25.0)
Pyrexia	3 (100.0)	3 (42.9)	49 (51.6)	55 (52.4)	4 (33.3)
AST increased	0	6 (85.7)	34 (35.8)	40 (38.1)	7 (58.3)
Cough	3 (100.0)	4 (57.1)	33 (34.7)	40 (38.1)	1 (8.3)
ALT increased	1 (33.3)	6 (85.7)	31 (32.6)	38 (36.2)	5 (41.7)
Diarrhoea	2 (66.7)	5 (71.4)	30 (31.6)	37 (35.2)	4 (33.3)
Upper respiratory tract infection	2 (66.7)	2 (28.6)	33 (34.7)	37 (35.2)	6 (50.0)
Anaemia	1 (33.3)	2 (28.6)	32 (33.7)	35 (33.3)	4 (33.3)
Neutrophil count decreased [a]	1 (33.3)	3 (42.9)	31 (32.6)	35 (33.3)	5 (41.7)
Constipation	1 (33.3)	2 (28.6)	25 (26.3)	28 (26.7)	3 (25.0)
Nasopharyngitis	0	1 (14.3)	25 (26.3)	26 (24.8)	0
Headache	1 (33.3)	3 (42.9)	18 (18.9)	22 (21.0)	2 (16.7)
Nausea	2 (66.7)	3 (42.9)	17 (17.9)	22 (21.0)	2 (16.7)
Leukocyte count decreased	1 (33.3)	2 (28.6)	16 (16.8)	19 (18.1)	3 (25.0)
Hypoglycemia	0	2 (28.6)	11 (11.6)	13 (12.4)	3 (25.0)
Pneumonia	0	0	10 (10.5)	10 (9.5)	3 (25.0)

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

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

Patients are counted once within each preferred term.
Reported AE terms were coded using MedDRA dictionary (Version 24.0).
Percentages are based on the total number of patients (N) specified in the column header.
Source: Module 5.3.5.3, PIP02 Report, Table 14.1.3.1/5 and Table 14.3.3.1/2

For most patients, the maximum severity of TEAEs were Grade 2 (30.5%) and Grade 3 (49.5%). There were 65 patients (61.9%) who experienced a TEAE of worst Grade 3 or 4, and these were considered related to larotrectinib in 30 patients (28.6%). Neutrophil count decreased was the only larotrectinib-related Grade 3 or 4 TEAE occurring in more than one patient (16 patients, 15.2%). There were no patients in the PIP02 SAF with a Grade 5 TEAE.

Forty-six patients (43.8%) experienced at least 1 SAE; those events occurring in 2 or more patients each were pyrexia, pneumonia, influenza, seizure, viral infection, vomiting, device related infection, diarrhea, gastroenteritis viral, headache, hydrocephalus, malaise, urticaria, vascular device infection, and wound infection.

Nine patients had 14 SAEs considered related to larotrectinib, including ejection fraction decreased and cardiac disorder (both events in 1 patient), abdominal pain, hematuria, hyponatremia, hypoventilation, malaise, pneumonia (in 1 patient each), hypernatremia (3 events in 1 patient), and vomiting (2 events) and irritability (both in 1 patient).

Six patients (5.7%) discontinued study treatment due to TEAEs; in two patients neutrophil count decreased led to discontinuation. Six patients died, all due to disease progression and none within 28 days after the last dose of larotrectinib, and for 5 of the patients the deaths were not during treatment or within 28 days after the last dose of larotrectinib. The date of death of 1 patient is unknown; however, the death occurred after disease progression and treatment discontinuation.

TEAEs are summarized by age group in Table 5. AE incidences were generally similar across the age groups.

TEAEs occurring in ≥20% of patients in any age subgroup and their relationship to larotrectinib are summarized in Module 5.3.5.3, PIP02 Report, Table 9-10. 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 both of the other age groups (children 2 to <12 years and adolescents 12 to <18 years): pyrexia, diarrhea, upper respiratory tract infection, neutrophil count decreased, and constipation.

Table 5. Overall adverse event information by age group (PIP02 SAF)

	Patient Incidence, n (%)			
Category of TEAE	**Infants and toddlers: birth to <24 months N = 43**	**Children: 2 to <12 years N = 45**	**Adolescent: 12 to <18 years N = 17**	**Total PIP02 SAF N = 105**
Any TEAE [a]				
All	42 (97.7)	45 (100.0)	16 (94.1)	103 (98.1)
Related to larotrectinib	36 (83.7)	40 (88.9)	10 (58.8)	86 (81.9)
Grade 3 or 4 TEAE [b]				
All	29 (67.4)	26 (57.8)	10 (58.8)	65 (61.9)
Related to larotrectinib	16 (37.2)	11 (24.4)	3 (17.6)	30 (28.6)
TEAEs resulting in study drug permanent discontinuation				
All	3 (7.0)	1 (2.2)	2 (11.8)	6 (5.7)
Related to larotrectinib	2 (4.7)	1 (2.2)	0	3 (2.9)
Serious TEAE				
All	18 (41.9)	19 (42.2)	9 (52.9)	46 (43.8)
Related to larotrectinib	2 (4.7)	4 (8.9)	3 (17.6)	9 (8.6)
TEAEs considered DLT	0	0	0	0
Fatal TEAE (Grade 5) [b]	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

[a] Only TEAEs are included. TEAEs are defined as adverse events that start or worsen on or after the first administration of study drug.

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

Percentages are based on the number of patients (N) specified in the column header.
Related events are those judged by the investigator as related to study drug.
Source: Module 5.3.5.3, PIP02 Report, Table 14.1.3.1/1 and Table 14.1.3.3/1

Adverse events of special interest

ALT and AST elevation

A total of 46 patients (44%) experienced treatment-emergent ALT/AST increase (based on PTs ALT increased, AST increased, and transaminases increased) of Grade 1 or higher. Grade ≥2 laboratory elevations were experienced by 11 patients; 1 patient had both Grade 2 and Grade 3 elevations, and 1 patient had a Grade 3 elevation.

For 5 patients, TEAEs of ALT increased and/or AST increased resulted in dose modifications (i.e., interruption or dose modification) in larotrectinib treatment. Most patients experiencing Grade 1 or 2 AST and/or ALT elevations continued treatment with larotrectinib through this laboratory finding.

Importantly, no patient met the Hy's Law criteria for drug-induced liver injury. Fifteen patients displayed a 3-fold or greater elevation in ALT relative to the ULN and 16 patients had a 3-fold or greater elevation in AST relative to the ULN. However, none of these patients had an out-of-range total bilirubin value, required for Hy's Law.

Neutropenia

The most commonly reported hematologic toxicity was neutrophil count decreased: shifts of 1, 2, 3 or 4 grades were experienced by 26, 11, 21 and 5 patients, respectively. At the last post baseline measurement, values in most patients had returned to baseline.

Neutropenia was reported as a TEAE in 35 patients (33.3%). The maximum severity was Grade 1 in 4 patients (4%), Grade 2 in 6 patients (6%), Grade 3 in 21 patients (20%), and Grade 4 in 4 patients (4%). Neutropenia was considered related to larotrectinib by the investigator in 26 patients (24.8%), but none was judged serious. Febrile neutropenia was reported as a TEAE in 1 patient. Generally, the neutropenia events occurred in the first 6 months of study treatment (23 out of 35 patients, 65.7%).

Of the 25 patients with treatment-emergent Grade 3 or 4 AEs of neutropenia, 19 patients had events that led to dose modification, including dose interrupted, modified, and discontinued. For the remaining 6 patients, the neutropenia resolved without study drug modification.

Neurologic events

Neurologic symptoms are a possible on-target toxicity from TRK inhibition. Neurologic events occurring in more than 3 patients overall were headache (22 patients), insomnia (9 patients), agitation (8 patients), dizziness (7 patients), irritability (6 patients), gait disturbance (5 patients), and presyncope, seizure, somnolence, anxiety, and restlessness (4 patients each). Assessment of these effects in children is complicated by its subjectivity and by difficulties with self-reporting.

Overall, 36 patients (34.3%) had TEAEs in the SOC Nervous system disorders and 34 patients (32.4%) in the SOC Psychiatric disorders. The majority of neurologic events were Grade 1 or 2 and were considered not related to larotrectinib treatment by the investigator.

A total of 10 (9.5%) patients had maximum Grade 3 or 4 neurologic events. Gait disturbance and headache were maximum Grade 3 in severity in 2 (2.1%) patients each. Other maximum Grade 3 neurologic events included hydrocephalus, irritability, paresthesia, peripheral motor neuropathy and peripheral sensory neuropathy in 1 patient (1.1%) each. Maximum Grade 4 neurologic events were hydrocephalus and seizure in 1 patient (1.1%) each.

The Grade 1 or 2 neurologic events that were considered related to larotrectinib included headache (5 patients, 4.8%), dizziness, insomnia, and agitation (2 patients, 1.9% each), and paresthesia, irritability, anxiety, and restlessness (1 patient, 1.0% each). One Grade 3 event of irritability was considered related to larotrectinib treatment; this event led to study treatment interruption and was

resolved before the data cut-off date. None of the other Grade 3 or 4 TEAEs were considered related to larotrectinib treatment.

One Grade 2 TEAE of motor dysfunction (a patient with primary CNS cancer) led to discontinuation of larotrectinib. Most neurologic events resolved under continued larotrectinib treatment, in the vast majority of patients without any dose reduction.

Palatability analysis set

The most common TEAEs were AST increased, upper respiratory tract infection, ALT increased, neutrophil count decreased, pyrexia, diarrhea, and anemia.

Pharmacokinetics

The pharmacokinetic analysis was based on blood samples collected on Cycle 1 Day 1 and Cycle 4 Day 1 at predose (only for Cycle 4 Day 1) and at 1 (±15 minutes) and 4 hours (±15 minutes) post-dose. Validated high performance liquid chromatography tandem mass spectrometry method was used to quantify the plasma larotrectinib concentrations.

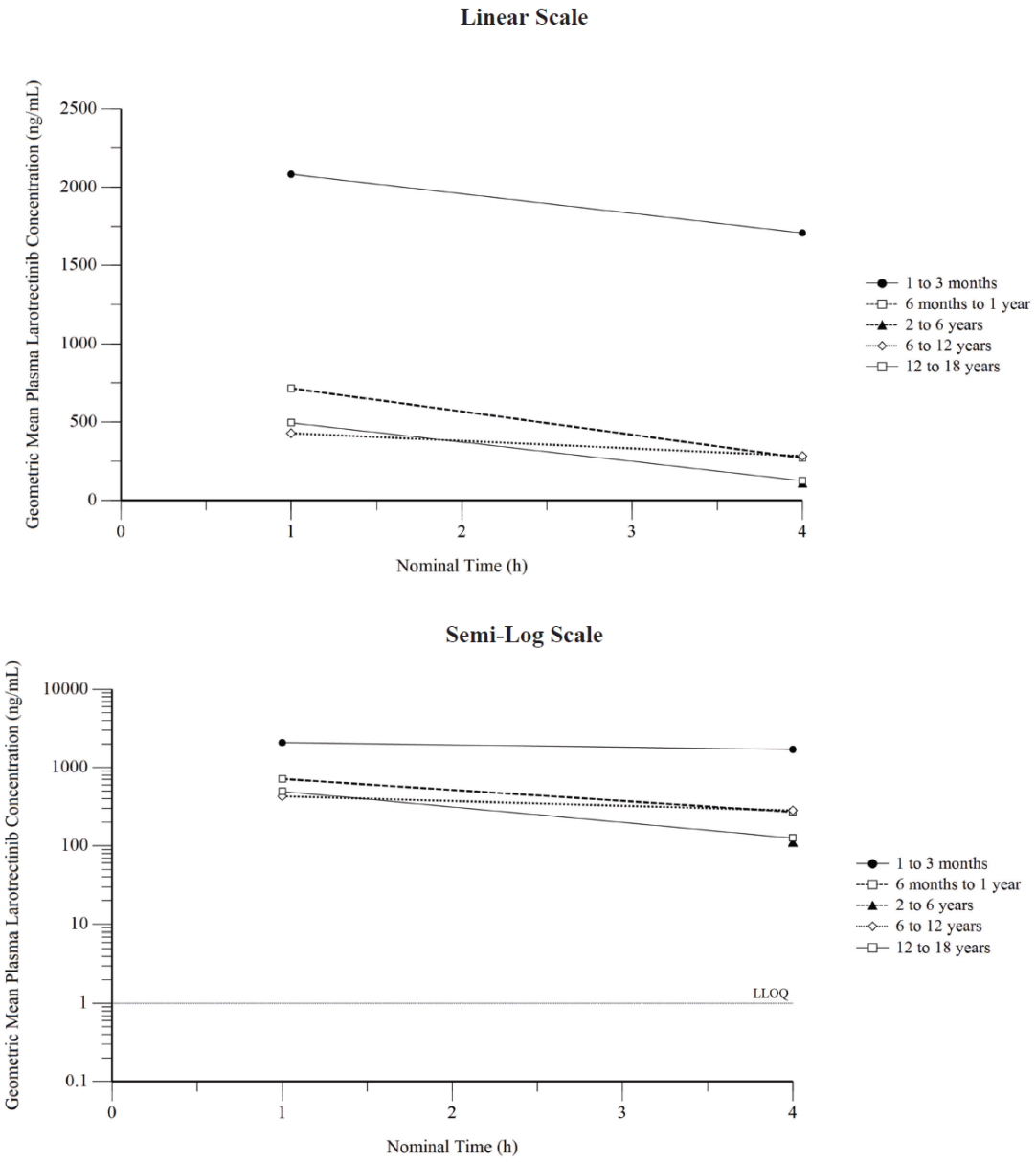
A non-compartmental analysis (NCA) was used to analyse the PK data and included calculation of several pharmacokinetic parameters such as overall exposure (AUC0-4 and AUC0-12) and plasma larotrectinib peak exposure (Cmax).

The PK analysis data set consisted of patients that received at least one dose of study drug and had sufficient plasma concentration data to assess at least one plasma PK parameter. The number of patients included in the PK analysis of Study 20290 in different age groups are shown in Table 6. The presented results are based on PK report BAYE-NCA-LARO-3697 dated 28 July 2022.

Table 6 List of Patients Included in the PK Analysis (Study 20290)

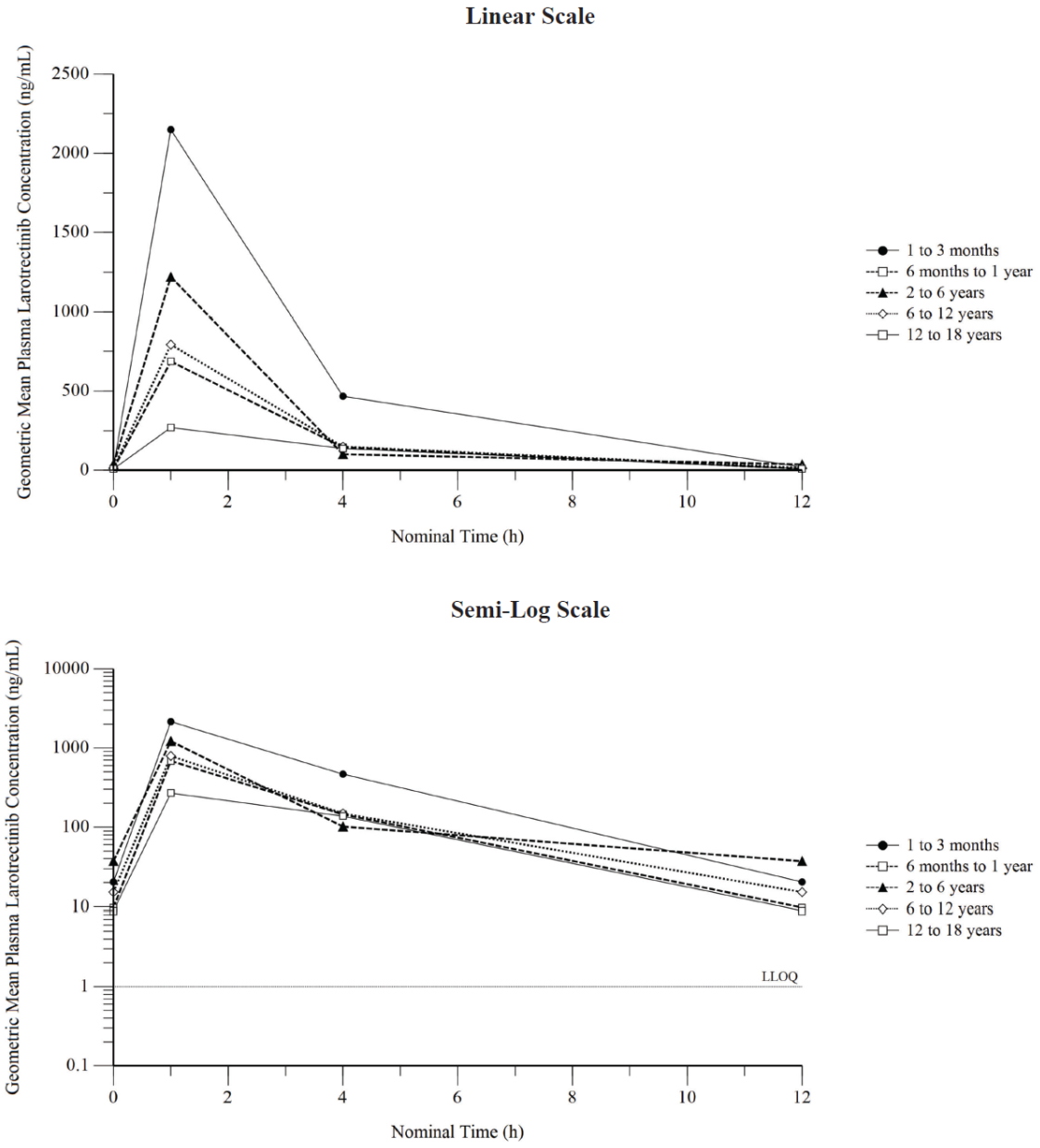
Pediatric age group	Number of patients			
	Data analysis set	PK analysis set		
	Overall N = 14	Overall N = 14	Cycle 1 Day 1 N = 14	Cycle 4 Day 1 N = 10
1 to 3 months	2	2	2	2
6 months to 1 year	2	2	2	2
2 to <6 years	1	1	1	1
6 to <12 years	4	4	4	3
12 to <18 years	5	5	5	2

The mean plasma concentrations vs nominal time are shown for Cycle 1 day 1 in Figure 6 and for Cycle 4 day 1 in Figure 7.



Note: The semi-log plot displays the lower limit of quantification (LLOQ) of 1.00 ng/mL. The age groups are: 1 to 3 months, 6 months to 1 year, 2 to < 6 years, 6 to < 12 years and 12 to < 18 years.
Source = Table 8.1.1.1 to Table 8.1.1.5

Figure 6 Geometric Mean Plasma Concentrations of Larotrectinib Following a Single Oral Administration of Larotrectinib in Pediatric Patients by Age Group – Phase 2 – Cycle 1 Day 1 (Linear and Semi-Log Scales)



Notes: The 12-hour concentration was imputed from predose concentration, if available. The semi-log plot displays the lower limit of quantification (LLOQ) of 1.00 ng/mL. The age groups are: 1 to 3 months, 6 months to 1 year, 2 to < 6 years, 6 to < 12 years and 12 to < 18 years.
Source = Table 8.1.1.6 to Table 8.1.1.10

Figure 7 Geometric Mean Plasma Concentrations of Larotrectinib Following Multiple Oral BID Administrations of Larotrectinib in Pediatric Patients by Age Group – Phase 2 – Cycle 4 Day 1 (Linear and Semi-Log Scales)

In summary,

• Plasma larotrectinib overall exposure (AUC0-4 and AUC0-12) for the youngest pediatric age group of 1 to 3 months was 4 to 6-fold higher in Cycle 1 Day 1 and 2- to 7-fold higher in Cycle 4 Day 1 compared with other age groups, while the oldest age group of 12 to 18 years showed the lowest exposure for both visits. Dose normalized AUC parameters followed a similar trend.

• Plasma larotrectinib peak exposure (Cmax) for the youngest pediatric age group of 1 to 3 months was 2- to 4-fold higher in Cycle 1 Day 1 and 2- to 10-fold higher in Cycle 4 Day 1 compared with other age groups, while the oldest age group of 12 to 18 years showed the lowest peak of exposure in both visits. Dose normalized Cmax parameters followed a similar trend.

• There was generally no plasma larotrectinib accumulation between Cycle 1 and Cycle 4, with the majority of pediatric age groups showing accumulation ratios for AUC0-4 (AR AUC0-4) between 0.68 and 0.88, except for the 2 to 6 years age group with value AR AUC0-4 of 1.4. However, note that this age group has limited data availability (N=1); therefore this result should be interpreted with caution.

• Geometric mean plasma larotrectinib CLss/F was the lowest for the youngest age group of 1 to 3 months, while the oldest age group of 12 to 18 years showed the highest value.

These data should be interpreted with caution, due to limited data availability per age group. The additional PK data was observed to be generally in the range observed for previous PK data in the respective age categories.

2.3.7. Extractables study for nasogastric tubes

The submission of the extraction studies for nasogastric tubes (NGT Study S21001492) is acknowledged. The conclusion drawn that the three alternative nasogastric feeding tube types investigated (polyurethane, polyvinyl chloride and silicone) are safe for their intended use of administration is supported.

2.3.8. MAH Conclusion

The results of the analyses of the patients evaluable for efficacy and safety in this PIP02 report were similar to the results of the full population in Study 20290. Larotrectinib demonstrated clinically meaningful antitumor activity in pediatric patients with locally advanced or metastatic solid tumors with NTRK gene fusions, with an overall response rate (ORR) of 84.3% and a median duration of response (DOR) of 31.4 months, as assessed by IRC. Larotrectinib demonstrated a favorable safety profile and was generally well tolerated.

Fourteen patients, who received the new age-appropriate oral solution, were included in the analysis presented in this report, of whom 12 were evaluable for efficacy and safety. No notable differences in efficacy results for patients receiving the new oral solution compared with the PIP02 population were observed. No unexpected new adverse events were reported for patients receiving the new oral solution.

With respect to PK, the youngest pediatric age group of 1 to 3 months had higher PK exposure compared with other age groups, while the oldest age group of 12 to 18 years showed the lowest PK exposure.

2.3.9. Discussion on clinical aspects

The PIP02 report evaluated treatment of pediatric patients from birth to less than 18 years of age with advanced solid tumors harboring an NTRK fusion, of all conditions included in the category of malignant neoplasms (except CNS tumors, hematopoietic and lymphoid neoplasms).

The PIP02 was based on Study 20290 which is an ongoing multicenter open-label Phase 1/2 study in pediatric patients aged from birth to 21 years with advanced solid or primary CNS tumors.

The main components of the PIP02 report were the efficacy, safety, pharmacokinetics (PK), and biomarker results in the PIP02 population based on Study 20290 (SCOUT) (N=105). I addition, efficacy

and safety results for 14 patients who were treated with the new age-appropriate solution in Study 20290 were described.

The ORR based on 89 evaluable patients was 84.3% (95% CI: [75.0, 91.1]). For the 12 efficacy evaluable patients in the palatability analysis set, the confirmed ORR was 66.7% (95% CI: [34.9, 90.1]).

The submitted efficacy, toxicity, tolerability and PK data is consistent with the known profile of Vitrakvi in paediatric patients.

No changes to the SmPC are proposed based on results from the PIP02 report; this is accepted.

3. CHMP overall conclusion and recommendation

Overall, the data do not change the positive benefit-risk-assessment for the medicinal product. Currently, available information in the SmPC regarding pediatric patients remains unchanged.

☐ **Fulfilled:**

☒ **Not fulfilled:**

"Not fulfilled" refers to the PAM. The data submitted was not intended to fulfil a PAM.

To get a compliance check of the PIP, the final data should be submitted to the PDCO in a compliance check procedure.

In the current procedure, there is no request for supplementary information.

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=98), Safety (N=105), PK (N=14), Biomarkers (N=38), 20 JUL 2021; Palatability / new oral solution (N=14) 08 APR 2022	28 Oct 2022
EPI VITRAKVI: A comparison of clinical outcomes in Infantile Fibrosarcoma (IFS) patients treated with larotrectinib in the phase I/II SCOUT study versus external historical cohorts	21767	Report Approval: 23 Sep 2022	28 Oct 2022