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Human Medicines Division

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

## VITRAKVI

Larotrectinib

Procedure no: EMA/PAM/0000338661

## 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** |
| ☐ | Submission deadline | 14 April 2026 | 20 March 2026 |
| ☐ | Start date | 27 April 2026 | 27 April 2026 |
| ☐ | CHMP Rapporteur AR | 1 June 2026 | 1 June 2026 |
| ☐ | CHMP comments | 15 June 2026 | 15 June 2026 |
| ☐ | Updated CHMP Rapporteur AR | 18 June 2026 | 18 June 2026 |
| ☒ | CHMP outcome | 25 June 2026 | 25 June 2026 |

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# 1. Introduction

On 20 March 2026, the MAH submitted a completed paediatric study for Vitrakvi, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH submitted a final report for:

- Study 20289 ("NAVIGATE"): A Phase 2 Basket Study of the Oral TRK Inhibitor Larotrectinib in Subjects with *NTRK* Fusion-Positive Tumours.

The MAH stated that Study 20289 is part of the clinical development program for Vitrakvi. The full data package was previously submitted with the original marketing authorisation application for Vitrakvi, when Study 20289 was still ongoing. The primary efficacy analysis of Study 20289 has, thus, been previously assessed and is described in the currently approved SmPC.

## *2.2. Information on the pharmaceutical formulation used in the study*

Larotrectinib is supplied as capsules (25 mg or 100 mg) or as an oral solution (20 mg/ml). Both of these formulations were used in Study 20289.

## *2.3. Clinical aspects*

### Introduction

Vitrakvi (larotrectinib) is an inhibitor of tropomyosin receptor kinases and thereby targets a specific oncogenic driver, neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions.

Larotrectinib received a Conditional Marketing Authorization in the EU on 19 September 2019, for a tumour-agnostic indication for the treatment of adult and paediatric patients with locally advanced or metastatic solid tumours harbouring a *NTRK* gene fusion.

The approved indication is:

> Monotherapy for the treatment of adult and paediatric patients with solid tumours that display an *NTRK* gene fusion:
>
> – who have a disease that is locally advanced, metastatic, or where surgical resection is likely to result in severe morbidity, and
>
> – who have no satisfactory treatment options.

A total of three studies is included in the development program for Vitrakvi (see Annex):

- Study 20288 (dose-finding study, finalised) did not include any paediatric patients.
- Study 20289 ("NAVIGATE") included a few paediatric patients and was finalised in September 2025 (last patient last visit).
- Study 20290 ("SCOUT") included paediatric patients and is still ongoing.

The MAH has now submitted the final study report for Study 20289 in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The MAH suggests that the paediatric data presented in the final report of Study 20289 does not warrant an update of the Product information.

## Clinical study

**Study 20289 ("NAVIGATE"): A Phase 2 Basket Study of the Oral TRK Inhibitor Larotrectinib in Subjects with NTRK Fusion-Positive Tumours**

## Description

Study 20289 was a Phase 2, multicentre, open-label study of patients with advanced solid tumours harbouring a gene fusion of *NTRK1, NTRK2*, or *NTRK3*. Patients with *NTRK* fusion-positive cancers were identified through molecular assays as routinely performed at CLIA, CAP-accredited, or other similarly certified laboratories.

The study consisted of a pre-screening period, screening period, treatment period, a safety follow-up visit, and long-term follow-up assessments.

## Methods

### *Study participants*

The study population consisted of male and female patients ≥12 years of age with locally advanced or metastatic malignancy with an *NTRK1, NTRK2*, or *NTRK3* gene fusion, who had received prior standard therapy appropriate for their tumour type and stage of disease or, in the opinion of the Investigator, were unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.

In some regions, patients <12 years could be included.

### *Treatments*

Larotrectinib was administered to patients at 100 mg BID as either oral capsule or solution and cycles were in 28-day increments.

Patients continued dosing of larotrectinib until disease progression, unacceptable toxicity, patients' withdrawal of consent, or death. Treatment beyond progression was allowed for patients deriving clinical benefit from continuing study treatment, based on Investigator's opinion and upon Sponsor's approval. Dose modifications were allowed.

### *Objective(s)*

The *primary objective* of the study was to determine the overall response rate (ORR) as determined by an independent radiology review committee

Secondary objectives included e.g. ORR as determined by investigators, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

### *Outcomes/endpoints*

ORR was defined as the proportion of patients with best objective response (BOR) of confirmed complete response (CR), pathological CR (pCR), or partial response (PR).

Safety analyses included treatment-emergent adverse events (TEAEs; defined as an adverse event [AE] that started on or after the first administration of study drug), serious adverse events (SAEs), AESIs, other AEs in focus, deaths, clinical laboratory parameters, and other safety evaluations.

No subgroup analyses by age group were performed.

### *Statistical Methods*

Descriptive statistics for continuous data included the number of observations (n), mean, standard deviation, median, minimum, and maximum. Discrete variables were summarized using the number of patients and percentages.

The point estimate of ORR was accompanied by a one-sided 90% exact binomial confidence interval (CI) using the Clopper-Pearson method.

## Results

### *Study subjects*

A total of 215 patients received at least 1 dose of larotrectinib. Six patients were paediatric patients (1 patient in the age group of 6 to <12 years and 5 patients in the age group of 12 to <16 years).

The median age of patients was 57.0 years (range 6 to 90 years).

The most common primary reason for study treatment discontinuation was disease progression (55%). The most common primary reason for study discontinuation was death (52%). At the time of the study completion, 64 patients (30%), still on larotrectinib treatment or in follow-up, had transitioned off-study as per protocol, and of these, 32 patients continued to receive larotrectinib treatment outside of this study through post-trial access program or other means.

### *Efficacy results*

Efficacy data for the six paediatric patients in Study 20289 were not presented separately. The Clinical Overview referred to an integrated efficacy analysis including data from the three key clinical studies, where data for paediatric and adult patients are presented separately. The integrated analysis was submitted within the ongoing Renewal procedure (EMA/R/0000335017) and will not be discussed here.

### *Safety results*

Safety data for paediatric patients in Study 20289 were not presented separately.

The Clinical Overview referred to an integrated safety analysis of paediatric data from Study 20289 and Study 20290. The integrated analysis was submitted within the ongoing Renewal procedure (EMA/R/0000335017) and will not be discussed here.

## Discussion on clinical aspects

Vitrakvi is approved for paediatric use. The primary efficacy and safety analysis of Study 20289 was previously assessed, during the original marketing authorisation application for Vitrakvi, together with

data from Study 20288 (which was previously finalised) and Study 20290 (which is still ongoing). The results are described in the approved SmPC.

With the current application, the final report of Study 20289 was submitted in accordance with Article 46, as it included paediatric patients.

Of a total of 215 patients that were treated with larotrectinib in the study, there were only six paediatric patients, of which 5 were in the age group 12 to <18 years and one was <12 years of age. Due to the low number of paediatric patients and as neither efficacy nor safety data for paediatric patients were presented separately in the study report, no new conclusions on the efficacy and safety of larotrectinib in paediatric patients can be drawn based on the final data from Study 20289 alone.

A potential update of the Product information regarding paediatric data should await completion of all studies in the development program, of which study 20190 is still ongoing.

# 3. Rapporteur's overall conclusion and recommendation

No new conclusions on the efficacy or safety of larotrectinib in paediatric patients with a malignancy with an *NTRK1, NTRK2*, or *NTRK3* gene fusion can be drawn based on the final report for Study 20289.

No update of the Product information is warranted.

## ☒ PAM fulfilled

No regulatory action required.

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

The studies should be listed by chronological date of completion:

## Clinical studies

| Study number, Conduct dates, Location | Protocol version implemented | Study design and objectives | Study drug doses |
|---|---|---|---|
| **Completed** | | | |
| **Study 20288** [a]<br><br>12 MAY 2014–<br>LPLV 09 APR 2021<br><br>US | 7.0 | Multicentre, Phase 1, open-label, 3 + 3 dose-escalation study in adult patients with advanced solid tumours.<br>Objectives were to determine the safety, including DLT, in adult patients with an advanced solid tumour, to characterize the PK properties, to describe the antitumor activity, and to identify the MTD and/or the appropriate dose of larotrectinib for further clinical investigation. | 50 to 200 mg/day (QD or BID)<br>Only 100 mg BID in expansion phase |
| **Study 20289**<br>NAVIGATE<br><br>30 SEP 2015–<br>LPLV 29 SEP 2025<br><br>North America,<br>Europe,<br>Asia Pacific,<br>South America | 13.0 | Multicentre, Phase 2, open-label "basket" study in patients 12 years of age [b] or older with an advanced cancer bearing an *NTRK* fusion.<br>The study included 9 cohorts of patients with tumours bearing somatic *NTRK* gene fusions of various tumour types, including NSCLC, thyroid cancer, sarcoma, CRC, salivary gland cancer, biliary cancer, primary CNS tumours, and others.<br>The primary objective was to determine the ORR, and the secondary objectives were to determine other efficacy parameters and to further assess the safety and tolerability of larotrectinib.<br>With protocol version 9.0 (08 OCT 2019), a new prospective cohort was to enrol up to 80 patients ≥18 years of age with lung cancer, melanoma, CRC, and non-secretory breast cancer (up to 20 patients per tumour type), and a minimum of 40 patients in other tumour types.<br>With protocol version 12.0 (15 MAR 2022), a new cohort for bone health assessment was introduced and was to recruit all tumour types, with at least 1 lesion, measurable or not measurable. | 100 mg BID |
| **Ongoing** | | | |
| **Study 20290** [a]<br>SCOUT<br><br>16 DEC 2015–<br>Ongoing<br><br>North America,<br>Europe,<br>Asia Pacific | 15.0 | Multicentre, Phase 1/2, open-label, dose-escalation study in paediatric patients (birth through 21 years) with advanced solid or primary CNS tumours.<br>The primary objective is to characterize the safety and DLT, and the secondary objectives are to characterize the PK, to identify the MTD or appropriate dose of larotrectinib for further study, and to describe the antitumor activity (ORR [primary endpoint] and other efficacy parameters) and pain and health-related | Dosing based on adult equivalent (50 to 150 mg BID), then 100 mg/m$^2$ BID (with a maximum of 100 mg BID) |

| Study number, Conduct dates, Location | Protocol version implemented | Study design and objectives | Study drug doses |
|---|---|---|---|
| | | quality of life.<br>With protocol version 14.0 (23 FEB 2022), a subcohort for new bone health assessment was introduced in the Phase 2 portion of the study. | |