26 March 2026
EMADOC-1700519818-3080621
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Retsevmo

International non-proprietary name: selpercatinib

Procedure No. EMA/VR/0000282012

Note

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

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

Term	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BID	twice daily
BOR	best overall response
BQL	below the quantification limit
BSA	body surface area
CI	confidence interval
CNS	central nervous system
CR	complete response
CSR	clinical study report
DOR	duration of response
FTC	follicular thyroid cancer
IRC	independent review committee
LLT	local laboratory tests
MA	marketing authorisation
MKI	multikinase inhibitor
MTD	maximum tolerated dose
MTC	medullary thyroid cancer
NCA	non-compartmental analysis

NE	not evaluable
NSCLC	non-small cell lung cancer
ODxTT	oncomine Dx target test
ORR	objective response rate
OS	overall survival
PFOS	powder for oral suspension
PFS	progression-free survival
PIP	paediatric investigation plan
PK	pharmacokinetics
PR	partial response
PT	preferred term
PTC	papillary thyroid cancer
RAI	radioactive iodine
rBA	relative bioavailability (study)
RECIST	Response Evaluation Criteria in Solid Tumours
RET	REarranged during Transfection
RP2D	recommended Phase 2 dose
RTU	ready-to-use
SD	stable disease
SmPC	summary of product characteristics
SMQ	standardised Medical Dictionary for Regulatory Activities Query
SOB	Specific Obligation
TC	thyroid cancer
TEAE	treatment-emergent adverse events
TE-SAE	treatment-emergent serious adverse event

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 27 June 2025 an application for a variation.

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include paediatric patients 2 years and older with: (1) Advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory, (2) Advanced RET-mutant medullary thyroid cancer, (3) Advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted, for RETSEVMO, based on final results from study J2G-OX-JZJJ (LOXO RET 18036, LIBRETTO-121); this is a multicentre, open-label Phase 1/2 study in paediatric patients with advanced solid or primary CNS tumours harbouring an activating RET alteration. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.6 of the SmPC are updated. The Package Leaflet and labelling are updated in accordance. Version 15.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the information related to Quality part of the dossier.

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau

Timetable	Actual dates
Submission date	27 June 2025
Start of procedure:	19 July 2025
CHMP Rapporteur's preliminary assessment report circulated on:	12 September 2025
Joint Rapporteur's updated assessment report circulated on:	9 October 2025

Timetable	Actual dates
Request for supplementary information and extension of timetable adopted by the CHMP on:	16 October 2025
MAH's responses submitted to the CHMP on:	27 November 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	5 January 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	23 January 2026
PRAC RMP advice and assessment overview adopted by PRAC	15 January 2026
2nd request for supplementary information and extension of timetable adopted by the CHMP on:	29 January 2026
MAH's responses submitted to the CHMP on:	20 February 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	12 March 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	19 March 2026
CHMP opinion:	26 March 2026
The CHMP adopted a report on similarity of Retsevmo with Lutathera, Onivyde pegylated liposomal, Zejula, Pemazyre, Kimmtrak, Xermelo, Qarziba, Ayvakyt, Koselugo, SomaKit TOC, Qinlock, Crysvita, Vyloy, Finlee, Elahere, Tibsovo, Hetronifly, Spexotras, Zynyz, Ogsiveo, Ziihera, Ojemda and Voranigo on:(Appendix 1)	26 March 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The applicant submitted an application for an extension of indication in paediatric patients 2 years and older with:

(1) Advanced *RET* fusion-positive thyroid cancer who are radioactive iodine-refractory,

(2) Advanced *RET*-mutant medullary thyroid cancer,

(3) Advanced *RET* fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted, patients who harbour a *RET* fusion-positive solid tumour, i.e histology-independent indication.

Disease or condition

RET-mutant medullary thyroid cancer

Medullary thyroid cancer (MTC) is associated with *RET* mutations in approximately 50% to 60% of adult patients but in over 90% of paediatric and adolescent patients (Eng et al. 1994; Hofstra et al.

1994; Agrawal et al. 2013; Paulson et al. 2019; Nies et al. 2021). Thyroid carcinomas may be more advanced and aggressive at presentation in children compared with the typical presentation in adults; otherwise, the pathophysiology appears to be the same regardless of age.

RET fusion-positive thyroid cancer

RET fusions are actionable oncogenic drivers that are identified in 6% to 9% of adult patients with papillary thyroid cancer (PTC) (Su et al. 2016; Kato et al. 2017). Although differentiated thyroid carcinoma, including PTC, is relatively rare in paediatric patients, it is the most common paediatric endocrine malignancy and presents with a higher incidence of *RET* fusions (25% to 30%; Paulson et al. 2019; Pekova et al. 2023) compared with PTC in adults.

Other RET fusion-positive solid tumours

In addition, *RET* gene fusions are observed in extremely rare subsets of other cancers, including breast, colon, esophageal, ovarian, prostate, stomach, pancreatic, salivary gland cancers (most occurring at rates of less than 1%) and in paediatric tumours such as infantile myofibromatosis and infantile fibrosarcoma. Limited data are available on the incidence of *RET*-altered cancers in paediatric patients other than those with thyroid cancer (GENIE cBIOPortal; Kato et al. 2017; Davis et al. 2020; Kohno et al. 2012, 2020; Santoro et al. 2020; Ballerini et al. 2012; Ju et al. 2012; Lipson et al. 2012; Takeuchi et al. 2012; Bossi et al. 2014; Stransky et al. 2014; Le Rolle et al. 2015).

State the claimed therapeutic indication

Retsevmo as monotherapy is indicated for the treatment of adults and ~~adolescents~~ paediatric patients ~~1~~2 years and older with:

- *advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)*
- *advanced RET-mutant medullary thyroid cancer (MTC), and*
- *advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit or have been exhausted.*

Epidemiology

For information on disease prevalence in the EU, please refer to the 'Clinical presentation' paragraph below.

There is no difference between adult and paediatric patients with regard to the types of alterations in *RET* resulting in the development of tumours. The mode of action of selpercatinib (inhibition of the RET kinase) is independent of the nature of kinase activation (fusion versus mutation) and the age of the patient (adult versus paediatric).

Biologic features

Genetic alterations in the *RET* gene have been implicated in the pathogenesis of several human cancers.

RET can become oncogenically activated through two primary mechanisms: 1) chromosomal rearrangements that fuse the RET kinase domain with a partner protein dimerization domain (e.g., Coiled-coil domain-containing protein 6 (CCDC6)/papillary thyroid cancer-1 (PTC1), Kinesin Family Member 5B (KIF5B), NCOA4/PTC3), producing hybrid proteins that endow the kinase with ligand-

independent, constitutive activity; and 2) point mutations that directly or indirectly activate the kinase (Drilon et al. 2018).

Clinical presentation

Thyroid cancers (MTC and TC)

There are few data available on the incidence of *RET*-altered cancers in paediatric subjects. Most of the available data concern TC. *RET* fusion–positive PTC and *RET*-mutant MTC have both been identified in paediatric patients and may be associated with worse outcome (Viola et al. 2014; Prasad et al. 2016). Available evidence indicates that 7% to 10% of all thyroid malignancies occur in children and young adults.

Differentiated thyroid carcinoma accounts for 4% of all paediatric cancers, and approximately 90% of children with differentiated thyroid carcinoma have PTC, whereas less than 10% are diagnosed with FTC (Nies et al. 2021). Approximately 6% of PTC in adults (Santoro et al. 2020; Su et al. 2016) and 22% to 45% of PTC in adolescents have been found to have *RET* fusions (Ortiz et al. 2020). *RET* fusions to date are extremely rare outside of PTC in children and the literature is limited to case level evidence. The largest case series includes 16 paediatric patients reported between 2015 and 2020 (Davis et al. 2020). Data suggest that all reported cases of *RET* fusion–positive cancers in children were diagnosed in patients aged less than 2 years or greater than 10 years with a male: female ratio of 1:1 (Davis et al. 2020).

Two meta-analyses were recently conducted for PTC and FTC, and 15 studies in total were selected for Europe, North America, and South America. The study reported a pooled global incidence rate of PTC and FTC in the paediatric age of 0.46 (95% CI: 0.33 to 0.59) and 0.07 (95% CI: 0.02 to 0.12) per 100,000 person-years, respectively (Moleti et al. 2023).

The incidence of MTC in the paediatric population is extremely low, with an estimated incidence in children of 0.03 per 100,000 population per year (SEER data) (Starenki and Park 2015; Zhao et al. 2020). In children, sporadic MTC is almost absent or described in anecdotal cases. In almost all children and young adults diagnosed with MTC, hereditary MTC syndromes are present and are known to be caused by missense mutation in the *RET* proto-oncogene (Viola et al. 2014).

Although rare, the most common form of TC in children is PTC. Several studies suggest that the increasing incidence of PTC and FTC is only partially accounted for by surveillance and enhanced detection, as there is also an increase in detection of large tumours and advanced-stage disease (Paulson et al. 2019). In addition, children with differentiated TC have a higher prevalence of gene rearrangements, likely as a consequence of increased follicular cell proliferation in this age group (Segni 2017; Desilets et al. 2023). Paediatric TC statistics are not widely available for many regions outside of the US, and there are no significant geographic variations expected in the incidence rates unless there has been specific environmental exposure, such as from radiation events like Chernobyl or Fukushima (Nakaya et al. 2022).

Other RET fusion–positive solid tumours

Besides *RET* fusion–positive TC, other *RET* fusion–positive cancers are not commonly seen in children and adolescents, and when they do occur, they might be relatively rare. The number of children and adolescents who have *RET* fusion–positive solid tumours is unknown (Pekova et al. 2023); thus, no direct comparison of the pathophysiology of these tumours in children and adults is possible. However, given the common mechanism of disease via constitutive RET activation, it is anticipated that RET inhibition can be a successful mode of treatment for these tumours across all age spectrums.

Management

Available therapies for paediatric patients with *RET*-activated cancers are focused on the treatment of localised or oligometastatic disease with surgery or radiation, which can cause permanent damage to surrounding normal tissues and other nearby organs. For some paediatric cancers, traditional chemotherapies or cytotoxic agents with poorly tolerable toxicity profiles may be recommended or approved by various histologies, but there are no approved targeted agents that minimise off-target toxicities for paediatric patients with *RET*-activated tumours.

At present, for patients aged 12 or over with advanced *RET*-activated thyroid cancer (MTC or PTC), selpercatinib as monotherapy is already authorised (i.e. first and second line).

No systemic agents are approved specifically for younger patients (aged 2 to 11) with advanced *RET*-fusion thyroid cancer, as well as for patients (aged 2 to under 18) with *RET*-activated solid tumours (regardless of histology).

Regarding children aged 5 years and older, vandetanib is approved for the treatment of unresectable locally advanced or metastatic mutant medullary thyroid cancer (MTC).

2.1.2. About the product

Selpercatinib is a first-in-class, selective, and potent small-molecule inhibitor of the REarranged during Transfection (RET) receptor tyrosine kinase with central nervous system activity. Oncogenic activation of RET via fusions or point mutations has been implicated in the pathogenesis of several human cancers affecting both adult and paediatric patient populations.

RETSEVMO (Selpercatinib) was granted a Conditional Marketing Authorisation (CMA) on 11 Feb 2021.

To date in Europe, selpercatinib monotherapy is indicated for the treatment of:

- Retsevmo as monotherapy is indicated for the treatment of adults with:
    - advanced *RET* fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a *RET* inhibitor
    - advanced *RET* fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted
- Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with:
    - advanced *RET* fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)
    - advanced *RET*-mutant medullary thyroid cancer (MTC)

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Table 1. Regulatory interactions in the EU for Retsevmo

Date	Additional Information
25 Feb 2019	Application for a PIP, including a request for a partial waiver and request for deferrals for selpercatinib.
8 Nov 2019	The EMA's Decision on the agreement of a PIP and on the granting of a waiver for selpercatinib (EMEA-002544-PIP01-18).
20 Dec 2019	MAA submission based upon LIBRETTO-001 data cut-off date of 17 Jun 2019 for the treatment of *RET* fusion–positive NSCLC, *RET* fusion–positive TC, and *RET*-mutant MTC.
11 Feb 2021	Commission adoption of the positive decision for granting a conditional MA for second-line treatment of *RET* fusion–positive NSCLC, *RET* fusion–positive TC and *RET*-mutant MTC.
30 Sep 2021	The EMA's acceptance on modification of an agreed PIP in relation to the timelines of PIP Study 1 (development of age-appropriate suspension formulation) (EMEA-002544-PIP01-18-M01).
02 Sep 2022	Commission Decision received for extension of indication to include first-line treatment of advanced *RET*-mutant MTC in adults and adolescents 12 years and older based on interim results from Study LIBRETTO-001 with a data cut-off date of 15 Jun 2021 (EMEA/H/C/005375/II/0014/G).
29 Nov 2022 and 30 Nov 2022	Submission of 2 Type II variations proposing to extend the selpercatinib indication to include the first-line treatment of adults and adolescents 12 years and older with advanced *RET* fusion–positive TC (EMEA/H/C/005375/II/0021) and adults with advanced *RET* fusion–positive solid tumours (EMEA/H/C/005375/II/0022). During the procedure for TC, Lilly submitted the interim CSR for LIBRETTO-121.
13 Apr 2023	The EMA's acceptance on modification of an agreed PIP in relation to changes to the age-appropriate formulation (Study 1), opening enrolment of LIBRETTO-121 (Study 7) and removal of need to collect pharmacodynamic markers in support of dose finding (EMEA-002544-PIP01-18-M02).
29 Feb 2024	Commission Decision received for the extension of the indication for the treatment of adults and adolescents 12 years and older with advanced *RET* fusion–positive TC (EMEA/H/C/005375/II/0021). This resulted in a Specific Obligation for LIBRETTO-121, final data due 30 Jun 2025.
29 Apr 2024	Commission Decision received for the extension of the indication for the treatment of adults with advanced *RET* fusion–positive solid tumours (EMEA/H/C/005375/II/0022).
17 Mar 2025	Submission of full and final PIP compliance check for selpercatinib including the results of the following studies: • PIP Study 1 – development of age-appropriate tablets • PIP Study 7 – LIBRETTO-121 • PIP Study 9 – Population PK model to simulate PK in paediatric subjects

Abbreviations: CSR = clinical study report; EMEA = European Medicines Evaluation Agency; MA = marketing authorisation; MAA = marketing authorisation application; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; PK = pharmacokinetics; PIP = paediatric investigation plan; RET = REarranged during Transfection; TC = thyroid cancer

In the framework of 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:

Number	Description	Due date
SOB 4	In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive thyroid cancer, the MAH should submit the final data from the study LIBRETTO-121.	30 June 2025
SOB 5	In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with systemic treatment naïve RET fusion-positive thyroid cancer, the MAH should submit the final data from the cohort 2 of the pivotal study LIBRETTO-001.	31 December 2025
SOB 6	In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive solid tumours other than NSCLC and thyroid cancer, the MAH should submit the final data from patients with RET-fusion positive solid tumours other than NSCLC and thyroid cancer enrolled in the pivotal study LIBRETTO-001.	31 December 2025

While the current application (EMA/VR/0000282012) was ongoing, SOB 5 AND SOB 6 were fulfilled as part of the annual renewal application (EMA/R/0000286890) that received CHMP opinion on 16 October 2025, and EC decision on 12 December 2025.

With the present application (EMA/VR/0000282012) the final data from LIBRETTO-121 (according to SOB 4) were submitted.

2.2. Quality

2.2.1. Introduction

The MAH is seeking approval for an extension of indication to include paediatric patients 2 years and older. Currently, selpercatinib is approved for adult and paediatric patients 12 years of age and older.

With the proposed extension variation, the applicant did not apply for any additional pharmaceutical form or strength of selpercatinib. Instead, the applicant provided updates to sections in Module 3 of the approved tablet application (EMEA/H/C/005375/X/0031) in order to provide information and quality data supporting the application for the paediatric indication.

Approved 40 mg tablet formulation is reminded hereafter:

The finished product is presented as immediate release film-coated tablets containing 40 mg of Selpercatinib.

The other ingredients are:

Tablet core: cellulose microcrystalline, mannitol, croscarmellose sodium, hydroxypropylcellulose, and sodium stearyl fumarate.

Film-coating agent: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, black iron oxide (E172) (40 mg)

The product is available in cold formable aluminium foil (CFAF) blisters sealed with aluminium foil lidding, in packs as described in section 6.5 of the SmPC.

The summary below details the information updated and added to Module 3. Only these sections have been updated. All other quality content of the eCTD Module 3 for the approved tablet remains unchanged.

- Under Section 3.2.P.2.2 additional information in support of paediatric development was provided as summarized:
- Information on paediatric formulation development of Selpercatinib Powder for Oral Suspension and Selpercatinib Ready to Use Suspension. Whilst the tablet formulation is already approved in the extension application for tablets EMEA/H/C/005375/X/0031, Lilly considered that this is relevant information to support the new paediatric indication, as it proposes to use tablets as the paediatric dosage form;
- The clinical trial materials used in clinical Study JZJJ/LIBRETTO-121, which is the study in which this indication application is based upon, and Study JZJU, which was conducted to support the development of the paediatric dosage form were included. A section was added to address formulation development for paediatric studies, including providing supporting information regarding the development of the paediatric dosage forms;
- 3.2.P.2.2.6 was added to provide an assessment of the acceptability of selpercatinib tablet drug product.
- Section 3.2.P.5.4 was updated to provide batch data for the clinical trial materials used in clinical Study JZJJ/LIBRETTO-121, which is the study in which this indication application is based upon, and Study JZJU, which was conducted to support the development of the paediatric dosage form.

Paediatric Development

Study LOXO-RET-18036 (J2G-OX-JZJJ), also known as LIBRETTO-121 (referred to Study JZJJ from here on), is a multicenter, open-label, Phase 1/2 study conducted in paediatric patients with advanced solid or primary central nervous system tumours harbouring an activating *RET* alteration. Oral formulations used in the study included capsules, tablets intact and dispersed, and a powder for oral suspension.

In the initial paediatric investigation plan (PIP), the development of a ready-to-use (RTU) suspension suitable for oral and feeding tube administration was proposed. Agreement was reached with PDCO for modification of the agreed PIP (EMEA-0002544-PIP01-18-M02, April 2023). The PIP modifications included agreement to develop an age-appropriate tablet dosage form. Content information of updated Sections under product development 3.2.P.2.2 were included as part of the Quality Overall Summary (QOS) documentation submitted in March 2025 to the European Medicines Agency (EMA) to check compliance with the agreed paediatric investigation plan as set out in the EMA's decision P/0133/2023 of 13 April 2023. The immediate release selpercatinib tablets are approved in 40 mg, 80 mg, 120 mg, and 160 mg strengths (EMEA/H/C/005375/X/0031) for the treatment of adults and adolescents 12 years and older. The sponsor provided justification for utilization of selpercatinib tablets by paediatric patients. The initially developed ready-to-use powder for oral suspension (PFOS) was found not convenient by paediatric patients in the clinical study JZJJ. For the limited number of paediatric patients who may have difficulty swallowing the tablet(s) or who require feeding tube administration, instructions for

an alternative preparation of the tablets were assessed in study JZJJ. The sponsor provided development information to support instructions for an alternative dosing administration using the tablets.. In the context of extension paediatric indication, acceptability of the tablet formulation was further assessed using questionnaires in Study JZJJ. The acceptability questionnaire for the tablet administered intact assessed the participant's ability to swallow the drug product. The acceptability questionnaire for the tablet dispersed for oral or feeding tube administration assessed the ease of preparing the dispersion and the administration experience, including palatability, if administered orally.

2.2.2. Discussion on quality aspects

Within the current application, the MAH for Retsevmo proposes to continue using the approved selpercatinib tablets (40 mg, 80 mg, 120 mg and 160 mg) for the paediatric population targeted by the applied extension of indication (2 years of age and older).

An epidemiologic information is provided to show that most of the paediatric patients can be trained to swallow the tablets. Nevertheless, for patients with difficulty in swallowing tablets, the SmPC recommends the use of multiples of 40 mg tablets to support method of administration.

The composition of the 40 mg tablet is reminded. The excipient composition is considered safe for the use in the youngest patients (2 years – 12 years).

An alternative administration strategy for selpercatinib tablet(s) was developed to support both oral and feeding tube administration in paediatric patients who cannot swallow the tablet(s) whole.

The alternative administration methods were proposed for experimentation in the Phase 1/2 LOXO-RET-18036 (J2G-OX-**JZJJ**), also known as LIBRETTO-121, clinical study. Acceptability of the tablet formulation, intact and dispersed, was investigated in the target population among paediatric patients and caregivers involved in this study.

After review the initially proposed alternative administration method has not been accepted (see Clinical aspects).

2.2.3. Conclusions on quality aspects

No change to the quality of the product has been proposed. Additional quality information has been provided in support of the application for the paediatric indication.

2.3. Non-clinical aspects

2.3.1. Introduction

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

As part of the paediatric development of selpercatinib, the MAH conducted a series of non-clinical juvenile animal studies (JAS) in rats. These were assessed by the CHMP as part of a previous application (EMEA/H/C/005375/II/0010). A summary of the main results is provided below:

Study LOXO-292-TOX-028: Juvenile rat toxicity study

A GLP-compliant study was conducted to determine systemic, neurobehavioral, and reproductive effects of selpercatinib when administered to juvenile male and female rats from Postnatal Day

(PND) 21 through PND 70 (study LOXO-292-TOX-028). This period of development in rats is considered approximately equivalent to age 2-12 in humans.

Justification of Route and Dose Levels

The route of administration was oral (gavage) because this is the intended route of clinical administration for humans.

Proposed doses for the juvenile study were 0, 30, 50, and 75 mg/kg/day (males) and 0, 50, 80, 125 mg/kg/day (females). These doses were selected based on the results of three dose range-finding studies (LOXO-292-TOX-019, LOXO-292 -TOX-022 and LOXO-292 -TOX-026) and a 1-month repeat dose study in adult rats (LOXO-292-TOX-001).

Experimental design

In study LOXO-292-TOX-028, a total of 40 rats per sex per group were assigned to the primary necropsy initially scheduled on PND71 (10/sex/group), recovery necropsy on PND98, and reproductive and behavioural assessments (20/sex/group). In addition, 24 treated rats per sex per group and 6 control rats/sex were assigned to the toxicokinetic phase.

The endpoints evaluated in that study were in line with the core battery described in the ICH S11 guideline.

Results

Moribundity was noted for high dosed males and females.

Treatment-related clinical observations noted from the mid dose level in both sexes, and were similar to those noted for the animals euthanized in extremis. They included: hunched posture, piloerection, unkempt appearance, cool body, red material on various surfaces, red penile discharge, soft faeces, partial closure of the eye(s), brown material in the anogenital area, salivation and/or clear material around the mouth, broken or missing incisor(s), thin body, broken tail, and/or prolapsed penis. These findings were generally noted in a dose-responsive manner throughout the dosing period.

In low-dosed males, limited occurrences of red material around the nose or in the urogenital area, broken incisors, and broken tail were observed. Treatment-related clinical observations that persisted into the recovery period included broken, missing, or malaligned incisors for all treated males and high-dosed females; red material on various body surfaces for mid- and high-dosed males and high-dosed females; hunched posture, piloerection and thin body for mid- and high-dosed males; and unkempt appearance and red penile discharge for high dosed males.

Treatment-related lower mean body weight gains with corresponding lower mean food consumption were noted in males and females in the mid and high dose groups compared to controls.

A treatment-related delay in the attainment of vaginal patency was noted in high dosed females (statistical significance vs. control group, and outside historical control range), together with a lower mean body weight value on the day of attainment related to effects on body weight noted above. There was not treatment-related effect on sexual maturation in males.

There was not treatment-related effect on neurobehavioural parameters evaluated in low and mid-dosed animals (due to excessive toxicity, this was not evaluated in high dosed animals).

Adverse effects on male reproductive performance were noted in mid-dose (50 mg/kg) males showing reduced fertility and copulation indices. These effects were attributed to those observed on reproductive organs, including: small, soft right and left testes and small right and left

epididymides; lower mean testis, epididymis, and cauda epididymis weights; degeneration of germinal epithelium and vacuolation of Sertoli cells in tests, and depletion of spermatozoa in epididymis; altered sperm parameters.

There was no effect on the reproductive performance of treated females mated with naïve males, estrous cycles, and intra-uterine survival (due to excessive toxicity, this was not evaluated in high dosed animals).

Changes in haematology (males: decreased reticulocytes at all dose levels, increased haemoglobin and haematocrit from mid dose levels; both sexes: increased MCV, MCH, RDW from mid dose level) and serum chemistry parameters (decreased total protein, albumin, and globulin at all doses; increased cholesterol, triglycerides, and phosphorus high dose levels) were reversed at the end of the recovery period.

Treatment-related alterations in bone densitometry/measurement were noted in males and females at all doses (≥30 and ≥50 mg/kg, respectively – high dosed animals not evaluated for bone parameters). They included generally dose-dependent effects on bone size/geometry mass and/or density at both the distal femur metaphysis and femur diaphysis, consistent with an impairment of bone modelling and a negative effect on the physis. At the end of the recovery period, males at all dose levels (≥30 mg/kg) and females at the mid dose level (80 mg/kg) presented persistent effects on bone size/geometry and density at both the distal femur metaphysis and femur diaphysis. At the distal femur metaphysis, some signs of reversibility (total and cortical/subcortical BMC did not persist) were noted in males at ≥ 30 mg/kg and in females at 80 mg/kg. Females at 50 mg/kg showed complete recovery of changes noted at both the distal femur metaphysis and diaphysis. In addition, males at 50 mg/kg and females at 80 mg/kg presented decreases in femur length reflecting the presence of an adverse effect on the physis at the end of the treatment period.

Overall, selpercatinib was not well tolerated in juvenile male and female rats at ≥30 mg/kg and ≥80 mg/kg, respectively. Adverse findings included moribundity for males at ≥50 mg/kg and for females at 125 mg/kg, clinical findings (hunched posture, thin body, piloerection, unkempt appearance, material on various body surfaces, and broken/missing incisors), lower body weights and body weight gains with reduced food consumption for males at ≥50 mg/kg and for females at ≥80 mg/kg. In addition, macroscopic and microscopic findings and alterations in organ weights were noted at ≥30 mg/kg for males and ≥80 mg/kg for females, and adverse alterations in bone densitometry/ measurement in males and females at ≥30 and ≥80 mg/kg, respectively. Adverse effects were also noted on spermatogenic parameters at 30 and 50 mg/kg and lower reproductive performance and intrauterine survival were noted when males at 50 mg/kg were mated with naïve females. Based on these results, a dose level of 50 mg/kg was considered to be the no-observed-adverse-effect level of selpercatinib when administered orally to female juvenile rats. A NOAEL could not be determined for male juvenile rats in this study.

2.3.2. Ecotoxicity/environmental risk assessment

The revised EMA guideline for environmental risk assessment (ERA) of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1 which came into effect September 2024) indicates that for Type II variations, the ERA dossier should be updated when there is an anticipated increase in the environmental exposure.

As a result, an updated ERA for the use of selpercatinib in Europe dated 16 June 2025 was provided.

The ERA was addressed with the aim of adding paediatric patients and taking into account the revised guideline for environmental risk assessment of medicinal products for human use.

Selpercatinib is currently authorised as RETSEVMO® as monotherapy for the treatment:

- of adults with:
    - advanced RET fusion-positive non-small cell lung cancer not previously treated with a *RET* inhibitor
    - advanced *RET* fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted
- of adults and adolescents 12 years and older with:
    - advanced *RET* fusion-positive thyroid cancer who are radioactive iodine-refractory
    - advanced *RET*-mutant medullary thyroid cancer (MTC)

With the current procedure, the applicant has requested to extend the following indications to include paediatric patients 2 years and above:

- advanced *RET* fusion-positive thyroid cancer who are radioactive iodine-refractory
- advanced *RET*-mutant MTC, and
- advanced *RET* fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted.

An ERA, including both Phase I and Phase II, and supporting data study reports were reviewed as part of a previous procedure (EMEA/H/C/005375/II/0022) which was submitted in November 2022 and approved in April 2024. This ERA is compliant with the EMA guideline CHMP/SWP/4447/00 corr 2 (June 2006).

Results from the ERA (Submission number EMEA/H/C/005375/II/0022) are provided below. No new studies were conducted as part of this application. Nevertheless, the results' tables below have been updated in accordance with the new template of the revised guideline.

Table 2. Summary of main study results: Phase I

Substance (INN/Invented Name):	Selpercatinib / Retsevmo®		
CAS-number (if available):	152628-33-4		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD 107	1.30 at pH 5 3.08 at pH 7 3.45 at pH 9	Potential PBT: N
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion

Bioaccumulation	log k_{ow}	1.30 at pH 5 3.08 at pH 7 3.45 at pH 9	potentially B
	BCF_{Kgl}	98 L/kgww 42 L/kgww	Not B
Persistence	Ready biodegradability	No	potentially P
	DT_{50} at 12°C	*Brandywine creek* Water 10 d Sediment 353 d DT_{50} whole system: 269 d *Choptank river* Water 9.8 d Sediment 348 d DT_{50} whole system: 338 d	vP
Toxicity	CLP Classification	Reproduction Category 1B	T
PBT/vPvB statement:	Selpercatinib is considered to be not PBT, nor vPvB		

Phase I			
Parameter	**Value**	**Unit**	**Conclusion**
$PEC_{sw, refined}$ *(*prevalence NSCLC+MTC+PTC* with RET*)*	0.034	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)			N

***NSCLC**: Non-Small Cell Lung Carcinoma +**MTC**: Medullary Thyroid Cancer +**PTC**: Papillary Thyroid Cancer

Table 3. Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	Test protocol	Result	Remarks
Water solubility at 20 °C	OECD 105	95.5 mg/L at pH 5 1.82 mg/L at pH 7 0.602 mg/L at pH 9	Shake flask
Ready Hydrolysis	OECD 111	>1 year	At pH 4, pH 7 and pH 9-Half-life
Adsorption-Desorption	OECD 106		

Soil 1 = Silt Clay Loam		Kads $_{FOC, soil\ 1}$ = 116,050 L/kg$_{oc}$	
Soil 2 = Sandy Loam		Kads $_{FOC, soil\ 2}$ = 341,959 L/kg$_{oc}$	
Soil 3 = Loamy Loam		Kads $_{FOC, soil\ 3}$ = 582,830 L/kg$_{oc}$	
Soil 4 = Clay Loam		Kads $_{FOC, soil\ 4}$ = 240,301 L/kg$_{oc}$	
Sludge 1 = Easton WWTP		Kads $_{FOC, soil\ 3}$ = 683 L/kg$_{oc}$	
Sludge 2 = Denton WWTP		Kads $_{FOC, sludge\ 1}$ = 1180 L/kg$_{oc}$	
Sludge 3 = Baltimore WWTP		Kads $_{FOC, sludge\ 1}$ = 1102 L/kg$_{oc}$	
Ready Biodegradability Test	OECD 314B	DT_{50} at 20°C: 3.46 d Adjusted to 12°C: DT_{50} at 12°C: 7.4 d not readily biodegradable	Biodegradation in Activated Sludge (28 d, 20°C)
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = Brandywine creek	OECD 308	$DT_{50, water\ 1}$= 4.7 d $DT_{50, sediment\ 1}$= 166 d $DT_{50, whole\ system\ 1}$= 127 d CO_2 = 0.47 % NER_{total} = 26.8 %	100 days-20 °C CO_2 and NER values at test end
Sediment 2 = Choptank river		$DT_{50, water\ 2}$= 4.6 d $DT_{50, sediment\ 2}$= 164 d $DT_{50, whole\ system\ 2}$= 159 d CO_2 = 0.50 % NER_{total} = 15.7 %	100 days-20 °C CO_2 and NER values at test end

Transformation products		>10% = *None*			*Major transformation products observed*
Phase II Aquatic effect studies					
Study type	Test protocol	Endpoint	Value	Unit	Remarks
Daphnia magna	OECD 202	NOEC	880	*µg*/L	Acute immobilization - 48h
Fish, *Pimephales promelas*	OECD 203	NOEC	1900	*µg/L*	Acute mortality 96h
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	NOEC	1700	*µg*/L	yield and growth rate, 72 h
Daphnia magna Reproduction Test	OECD 211	NOEC	97	*µg*/L	*21-day chronic growth, reproduction, and survival*
Fish *Pimephales promelas*	OECD *210*	NOEC	160	*µg*/L	*4-day embryo + 28 day posthatch, chronic growth and survival)*
Activated Sludge, sewage microorganisms Respiration Inhibition Test	OECD 209	NOEC	1,000,000	*µg*/L	respiration inhibition, 3 h
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/*Chironomus riparius*	OECD 218	NOEC	298	mg/kg_{dw}	28-day chronic emergence rate and development rate.
Phase II Secondary poisoning					
Bioaccumulation Test in fish /*Lepomis macrochirus* Test 1 = 13.2 µg/L Test 2 = 136 µg/L	OECD 305	$BCF_{kinetic.}$ growth, corrected. lipid-normalized $BCF_{kinetic.}$ growth, corrected. lipid-normalized	98 42	L/kg L/kg	normalised to 5% lipids
Risk characterisation					
Compartment	PEC	PNEC	RQ		Conclusion
STP	0.34 µg/L	100,000 µg/L	0.0000034		No risk

Surface water	0.034 µg/L	9.7 µg/L	0.0035	No risk
Groundwater	0.0085 µg/L	0.97 µg/L	0.0088	No risk
Sediment	1.09 mg/kg_{dw}	20 mg/kg_{dw}	0.055	No risk

Assessment of paediatric data on non-clinical aspects

Since the determination of prevalence of the indications used to estimate exposure to the environment in the ERA was not refined for age, the predicted environmental concentrations will not change with the addition of paediatric patients of 2 years and above.

2.3.3. Discussion on non-clinical aspects

The definitive juvenile toxicity study (study LOXO-292-TOX-028) that supports a paediatric indication for selpercatinib, was submitted and assessed by the CHMP as part of the procedure EMEA/H/C/005375/II/0010. It was initiated in rats aged 21 days at 30 to 75 mg/kg/day and 50 to 125 mg/kg/day in males and females, respectively. These dose levels induced exposure levels 1- to 5-fold higher those at the MRHD in adults. According to the toxicokinetic data, there was no over-exposure of animals at PND21 vs. PND64/70 and exposure increased generally in a dose-related manner.

There were adverse effects on the **developing skeleton** characterized by adverse non-reversible histopathological changes at growth plates (physeal dysplasia) associated with decreased long bone (femur) length at the recovery necropsy, and non-reversible changes in bone densitometry parameters at femur metaphysis and diaphysis. These findings were observed at all doses in treated males and from the mid-dose level in females, corresponding to exposure levels within those reached in adult patients (x1.2-4.9 in males, x2.7-3.7 in females). At the low dose level in females, the exposure ratio was 1.3. Overall, there is no safety margin for skeletal changes reported in that study which may be relevant in paediatric patients with open growth plates.

In addition, **reproductive performance** was impaired in male rats mated to naïve female rats after completion of neurobehavioural assessments (i.e. after PND95), as shown by decreased fertility and copulation indices, increased pre- and postimplantation loss, and decreased viable embryos at 50 mg/kg/day (mid dose level). This was associated with altered sperm quality and non-reversible histopathological changes in testes/epididymides (degeneration of germinal epithelium, vacuolation of Sertoli cells, and depletion of spermatozoa in epididymis) at all dose levels.

Sexual maturation was delayed in females at the high dose level of 125 mg/k mg/kg (x3.5-5.3 clinical exposure), while estrous cycle and reproductive performance were not affected by treatment when evaluated at doses up to 80 mg/kg (x2.7-3.5 clinical exposure).

As a result of the Retsevmo II-10 procedure, main non-clinical findings were incorporated into section 5.3 of the SmPC ('Juvenile toxicity').

Following the skeletal findings in non-clinical studies, the MAH submitted as part of a separate application (Retsevmo II-30), a review on events of slipped capital femoral epiphysis (SCFE) or slipped upper femoral epiphysis (SUFE) reported in paediatric patients with selpercatinib and updated sections 4.4 and 4.8 of the SmPC in order to add a new warning on 'Epiphysiolysis of the femoral head in Paediatric Patients' and to add it to the list of adverse drug reactions (ADRs) with frequency 'Common'. See also the Clinical safety section of this report.

Environmental risk assessment

The variation EMEA/H/C/005375/II/0022 assessed the environmental risk of selpercatinib for thyroid cancer (medullary/papillary) and lung cancer (NSCLC) in adults/adolescents (>12 years). The assessment used conservative 3-year prevalence data, without refining for cancer stage, previous chemotherapy, or adult use. It was concluded that selpercatinib poses no significant environmental risk and is not classified as PBT (persistent and bioaccumulative and toxic) or vPvB (very persistent and very bioaccumulative).

Concerning the current Type II variation, the inclusion of paediatric patients (≥2 years) to the therapeutic indication does not alter predicted environmental concentrations (PECs), as the original prevalence data was not age-specific. No new studies were required.

Although no updated ERA dossier is required to support the inclusion of paediatric patients, the existing data was reviewed under the revised ERA guideline (CHMP/SWP/4447/00 2024).

Key findings include:

- Secondary poisoning: not required, as the Bioconcentration Factor (BCF) in fish is $< 100\ L \cdot kg^{-1}$.
- Groundwater risk: the revised PNEC is $0.97\ \mu g \cdot L^{-1}$ (previously $9.7\ \mu g \cdot L^{-1}$), but the PEC ($0.0085\ \mu g \cdot L^{-1}$) remains below this threshold.

These differences would not change the conclusions on environmental risk.

2.3.4. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of selpercatinib. Considering the above data, selpercatinib is not expected to pose a risk to the environment.

2.4. Clinical aspects

GCP

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

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 4. Tabular overview of clinical studies

Study ID; Location of Report; Study Status	Study Title and Description	Study Objectives or Outcomes	Patient, Study Participant, or Tumor Population	Number of Treated Participants
Registration study				
Study ID: LOXO-RET-18036 (Study J2G-OX-JZJJ; LIBRETTO-121) **Study status**: Ongoing (primary objective DBL: 12 December 2024)	A Phase 1/2 study of the oral RET inhibitor LOXO-292 in pediatric patients with advanced RET-altered solid or primary central nervous system tumors **Key design features:** • Multicenter • Multicohort • Open-label • Single arm • Dose escalation followed by dose expansion	**Phase 1** ***Primary objective*:** To determine safety profile including DLTs. ***Secondary objectives***: • To determine MTD and/or RP2D • To assess o PK o ORR, and o CBR **Phase 2** ***Primary objective***: To assess ORR by IRC ***Secondary objectives***: To assess • ORR by INV • DOR, PFS, CBR, and best change in tumor size by IRC and INV • OS • safety and tolerability, and • PK	PTC MTC Other cancers Total	15 15 6 36
Supporting studies				
Study ID: J2G-OX-JZJO **Study status**: CSR completed (DBL: 02 February 2022)	An open-label taste assessment of selpercatinib in healthy panelists	***Objective*** Evaluate the palatability (basic tastes, aroma, texture, and mouth feel) of selpercatinib oral	Not applicable (healthy panelists)	10
	Key design features: • Phase 1 • Open-label • Multiple dose	formulation prototypes (alone or dispersed in food dosing vehicles) to optimize the palatability and support the development of a dosage form suitable for intended adult or pediatric population		
Study ID: J2G-MC-JZJU **Study status:** EMP CSR completed (LPLV: 18 March 2022)	An open-label, randomized study to evaluate the relative bioavailability of selpercatinib in 3 formulations for pediatric use **Key design features:** • Phase 1 • Open-label • Randomized • 3-Formulation, 3 period cross over study	***Primary objective:*** To evaluate the relative bioavailability of RTU and PFOS suspensions compared to the capsule formulation ***Secondary objectives:*** • To evaluate the safety and tolerability of a single 20-mg oral dose of selpercatinib RTU and PFOS suspensions • To assess the palatability of selpercatinib RTU and PFOS suspensions	Not applicable (overtly healthy participants)	42

Abbreviations: CBR = clinical benefit rate; CSR = clinical study report; DBL = database lock; DLT = dose-limiting toxicity; DOR = duration of response; INV = investigator; IRC = independent review committee; LPLV: last patient last visit; MTC = medullary thyroid cancer; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFOS = powder for oral suspension; PK = pharmacokinetic; PTC = papillary thyroid cancer; RP2D = recommended Phase 2 dose; RTU = ready to use.

2.4.1. Clinical pharmacology

2.4.1.1. Pharmacokinetics

Selpercatinib is an orally available, highly selective, adenosine triphosphate (ATP)-competitive small molecule inhibitor of the RET receptor tyrosine kinase.

Selpercatinib is indicated for the treatment of adult patients with RET fusion-positive NSCLC, RET fusion-positive solid tumours and TC, RET-mutant MTC. Selpercatinib is also indicated for the treatment of adolescent patients aged 12 years and older with RET fusion-positive TC and RET-mutant MTC.

In Europe, two strengths of selpercatinib hard capsules, 40 and 80 mg, are available. Following EMEA/H/C/005373/X/0031, additional four strengths of selpercatinib tablets, 40, 80, 120 and 160 mg were made available, in order to minimize the size of the dosage form as well as the quantity of dosage units.

Selpercatinib is orally given and the recommended dose is based on body weight:

- Less than 50 kg: 120 mg twice daily.
- 50 kg or greater: 160 mg twice daily.

In the current application, the MAH seeks approval to extend the indications of selpercatinib cited above (except NSCLC) to paediatric patients 2 years of age and older. This application is covered by EMEA-002544-PIP01-18-M02.

No age-appropriate formulation is claimed, therefore both capsule and tablet formulations apply.

In paediatric patients aged 2 years to less than 12 years, the recommended dose proposed by the MAH was based on body surface area (BSA) categories (Table 5).

Table 5. Recommended dose for paediatric patients 2 to less than 12 years of age

Body surface area (BSA)	**Recommended dose**
0.33 to 0.65 m^2	40 mg three times daily
0.66 to 1.08 m^2	80 mg twice daily
1.09 to 1.52 m^2	120 mg twice daily
≥1.53 m^2	160 mg twice daily

To support this extension of indications for children aged 2 to less than 12 years, the MAH submitted:

- Study **J2G-MC-JZJU**: a relative bioavailability (rBA) study
- Study **J2G-OX-JZJJ** (**LIBRETTO-121**, data cutoff 08 Nov 2024) performed in children and adolescent aged 2 to 18 years where selpercatinib was administered as an oral liquid suspension or in capsule/tablet BID. was submitted,
- A new population PK (PPK) analysis was performed.

Bioanalytical methods

Two bioanalytical methods were used to quantify selpercatinib in human samples for study **J2G-OX-JZJJ** (TM17-410 validated in 2018) and study **J2G-MC-JZJU** (TM19-544 validated in Oct 2019). Both methods are identical and differ by their validated assay ranges, 1 to 1000 ng/ml and 10 to 10000 ng/mL respectively. Both bioanalytical methods were validated according to current guideline (EMA 2011).

In study validation J2MG-MC-JZJU

A total of 2410 samples were received between 15 Feb 2022 to 24 March 2022. All samples were analysed within 99 days of collection. 62 samples were reanalysed due to STD1 invalid (LLOQ set at 20 ng/mL when invalid (STD2), LLOQ set at 10 ng/mL when STD1 was valid). A total of 180 study samples were re-analysed for ISR and 98.9% were within ±20%.

In study validation J2G-OX-JZJJ

No bioanalytical report was provided. As stated by the applicant the two methods named TM17-410 and TM19-544 used to quantify selpercatinib in human samples were previously used for other applications and are considered validated for the purpose.

Statistical methods

Standard non-compartmental PK parameters were computed using Phoenix WinNonlin 64 Build 8.3.5 (Certara Corporation, Radnor, PA, USA). The following PK parameters were calculated from concentration data from plasma concentrations determined on C1D1, C1D8, and C3D1, if feasible (AUC12h, AUC24h, Cmax, Tmax, CLss/F, RaCmax)

The PPK analyses and simulations were performed using nonlinear mixed-effects modelling software NONMEM (version 7.5.0) using the FOCEI method, supplemented with Perl-speaks-NONMEM (PsN), version 5.3.0. Rsoftware version 4.3.1 was used for scripting, data management, GOF and model evaluation.

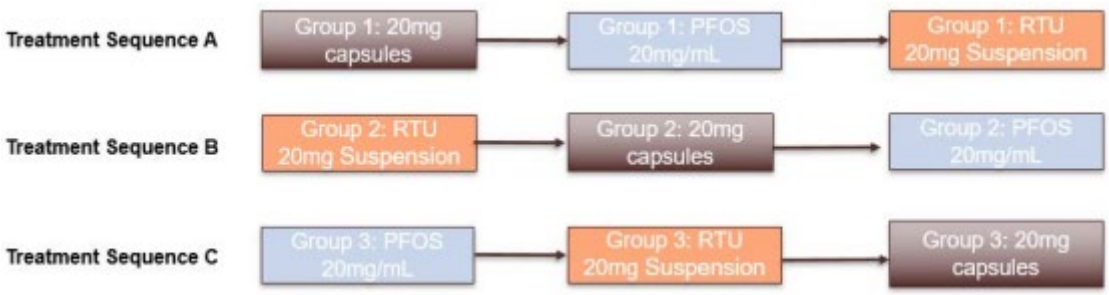
Biopharmaceutic study J2G-MC-JZJU

Study **J2G-MC-JZJU** was an open-label, randomised, three formulations, three periods, crossover to compare the ready to use 20 mg suspension formulation, the powder for oral suspension (PFOS) and the 20 mg capsule formulation in healthy male and female participants.

Design

Participants were screened within 28 days before enrolment, and admitted to the clinical research unit on Day -1. On Day 1 participants were randomised to 1 of the 3 treatment sequences as shown in the figure below, and received single doses of selpercatinib on Day 1, 8 and 15 as one of the three formulations (suspension, PFOS, capsule) in the fast state. A wash-out period of 7 days was considered.

Figure 1. Study J2G-MC-JZJU design



RTU = Ready to use
PFOS = Powder for oral suspension

Participants were required to be aged between 18 and 65 years with a BMI of 18 to 35 kg/m^2 at screening.

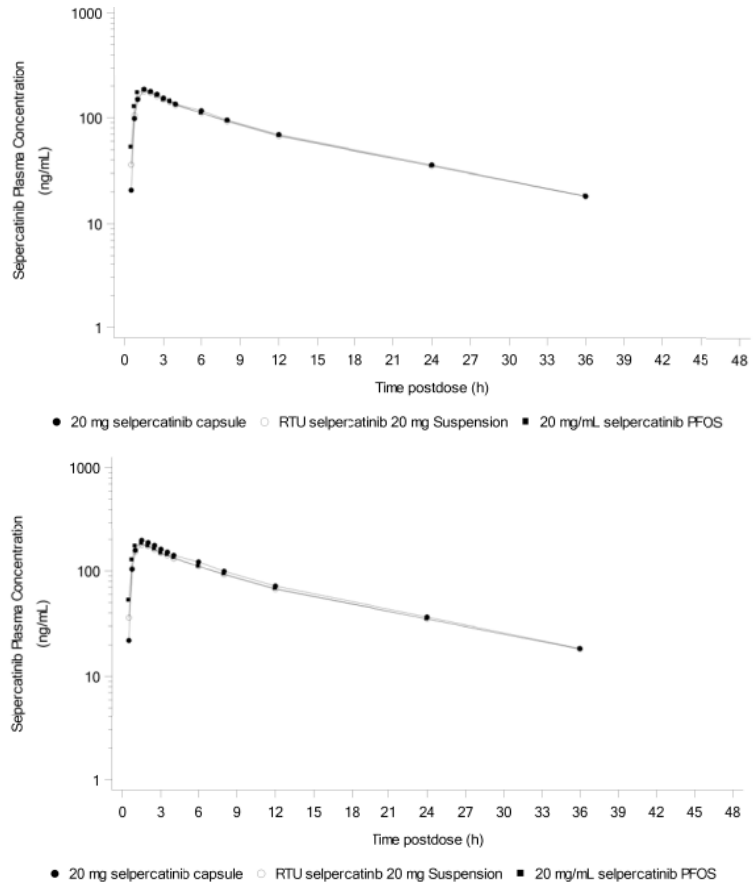
PK sampling consisted of pre-dose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120 and 144 h post-dose.

A total of 42 participants were enrolled, with 39 participants receiving all dose and 38 completed the study. rBA results are presented in Figure 2, associated PK parameters in Table 6, and statistical analysis in Table 7.

Table 6. Summary of PK parameters of selpercatinib

Parameter	Geometric mean (Geometric CV%) [n] 20 mg selpercatinib capsule (N=39)	RTU selpercatinib 20 mg Suspension (N=41)	20 mg/mL selpercatinib PFOS (N=41)
AUC(0-tlast) (ng.h/mL)	2180 (36.9%) [38]	2160 (31.6%) [41]	2190 (30.8%) [41]
AUC(0-∞) (ng.h/mL)	2540 (28.0%) [36]	2410 (29.0%) [41]	2490 (27.0%) [40]
Cmax (ng/mL)	176 (64.2%) [38]	174 (36.9%) [41]	180 (39.8%) [41]
tmax (h)#	1.50 (1.00-24.02) [38]	1.50 (1.00-3.00) [41]	1.50 (1.00-3.50) [41]
t1/2 (h)~	11.4 (7.08-18.1) [36]	11.9 (7.56-19.1) [41]	12.1 (8.09-27.6) [41]
CL/F (L/h)	7.86 (28.0%) [36]	8.31 (29.0%) [41]	8.05 (27.0%) [40]
Vz/F (L)	129 (25.1%) [36]	142 (30.3%) [41]	138 (33.4%) [40]
Vss/F (L)	129 (28.7%) [36]	141 (32.9%) [41]	136 (33.9%) [40]

Figure 2. Arithmetic mean plasma concentration profiles of selpercatinib for study J2G-MC-JZJU (up: RTU vs capsule; down PFOS vs capsule)



RTU = Ready to use
PFOS = Powder for oral suspension

Table 7. Statistical analysis of PK parameters of selpercatinib

Parameter	Treatment	n	Geometric least squares mean	Ratio of geometric least squares mean (Test:Reference)	90% CI for the ratio (Lower, Upper) [P-value]
AUC(0-tlast) (ng.h/mL)	Capsule (Reference)	38	2122		
	RTU (Test)	41	2151	1.01	(0.972, 1.06) [0.5997]
	PFOS (Test)	41	2196	1.03	(0.992, 1.08) [0.1800]
AUC(0-∞) (ng.h/mL)	Capsule (Reference)	36	2425		
	RTU (Test)	41	2399	0.989	(0.953, 1.03) [0.6221]
	PFOS (Test)	40	2471	1.02	(0.982, 1.06) [0.4024]
Cmax (ng/mL)	Capsule (Reference)	38	174		
	RTU (Test)	41	174	1.00	(0.937, 1.08) [0.9141]
	PFOS (Test)	41	180	1.04	(0.968, 1.11) [0.3747]

Study J2G-OX-JZJJ (LIBRETTO-121)

Study **J2G-OX-JZJJ** (**LIBRETTO-121** or **LOXO-RET-18036**) was a multicentre, open-label, Phase 1/2 study in paediatric patients with advanced solid or primary CNS tumours harbouring an activating *RET* alteration.

Design

The purpose of this study was to understand the PK, safety and maximum tolerated dose (MTD) of selpercatinib in paediatric patients and to permit the preliminary assessment of efficacy. This study includes two parts, a dose escalation (Phase 1) and a dose expansion (Phase 2). Objectives of the study (a part PK) are presented in Clinical efficacy and safety sections of this report.

Phase 1: Dose escalation and MTD determination

Selpercatinib was administered orally BID, with a BSA-based dose. The starting dose level of 92 mg/m^2 BID (maximum 160 mg BID) was intended to deliver equivalent exposure to the RP2D in adults as shown in Table 8.

Table 8. Study intervention administered

<table>
<tr><th>Parameter</th><th>Treatment Administered</th></tr>
<tr><td>Intervention name</td><td>Selpercatinib (LY3527723)</td></tr>
<tr><td>Type</td><td>Investigational drug</td></tr>
<tr><td>Dose formulation</td><td>Liquid suspension or simple blend capsules/tablets containing drug substance with a simple blend of excipients</td></tr>
<tr><td>Dosage level</td><td>Phase 1: Dose-finding and dose-escalation phases
<table>
<tr><th>Dose Level</th><th>Dose</th><th>Estimated Equivalent Adult Dose</th></tr>
<tr><td>-2</td><td>46 mg/m^2 BID</td><td>80 mg BID</td></tr>
<tr><td>-1</td><td>70 mg/m^2 BID</td><td>120 mg BID</td></tr>
<tr><td>1[a]</td><td>92 mg/m^2 BID</td><td>160 mg BID</td></tr>
<tr><td>2[a]</td><td>116 mg/m^2 BID</td><td>200 mg BID</td></tr>
<tr><td>3[a,b]</td><td>140 mg/m^2 BID</td><td>240 mg BID</td></tr>
</table>
Phase 2: Patients in Phase 2 received selpercatinib at the MTD or RP2D
Maximum dose in Phase 2 is 160 mg BID</td></tr>
<tr><td>Route of administration</td><td>Orally or via nasogastric or gastrostomy feeding tube.</td></tr>
<tr><td>Sourcing</td><td>Provided by Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company (Sponsor)</td></tr>
</table>

Abbreviations: BID = twice daily; MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose; SRC = Safety Review Committee.

[a] The dose levels listed, that is, Dose Levels 1, 2, and 3 correspond to the Phase 1 dose Cohorts 1, 2, and 3, respectively.

[b] Additional dose escalation may be considered based on the cumulative data (PK, safety, and efficacy); the actual dose determined by the SRC, not to exceed approximately 50% of the prior dose and considering capsule doses and capsule burden.

Phase 2: opened to enrolment when the MTD/RP2D was confirmed and enrolled patients into 1 to 4 cohorts as shown in Table 20, in the Clinical efficacy section.

PK sampling consisted of T2h and 4h at C1D1, pre-dose, 1, 2, 4 and 8h post dose at C1D8 and C3D1.

Results

During Phase 1, only Dose 1 was delivered. As Dose 1 became the RP2D, all Phase 1 and Phase 2 patients were analysed together for PK, efficacy and safety.

A total of 36 patients from Phase 1 and Phase 2 were treated with at least 1 dose of selpercatinib, 15 with MTC, 15 with PTC and 6 were *RET*-altered non-TC.

In Phase 1, one patient was aged 18-<21 years, one patient 12-<18 years and one aged 6-<12 years. An additional patient aged 2 years was enrolled but subsequently categorised as a Phase 2.

In Phase 2 cohort: 3 patients were aged 2-<6 years, 7 patients were aged 6-<12 years, 19 patients were aged 12-<18 years, and 4 patients were aged 18-<21 years.

Details on the demographic of the patients enrolled is presented in Table 9. The median age was 13 years (min-max: 2-20 years).

Table 9. Patient Demographics (J2G-OX-JZJJ study)

	Total (N=36)	MTC (N=15)	PTC (N=15)	Other (N=6)
Age at Informed Consent/Assent (years)				
n	36	15	15	6
Mean	12.5	12.8	13.2	10.0
Standard Deviation	4.75	5.31	4.09	4.82
Median	13.0	13.0	12.0	9.5
Minimum	2	2	6	5
Maximum	20	20	20	15
Age Group (n, %)				
2 years to <6 years	3 (8.3)	2 (13.3)	0 (0.0)	1 (16.7)
6 years to <12 years	8 (22.2)	3 (20.0)	3 (20.0)	2 (33.3)
12 years to <18 years	20 (55.6)	7 (46.7)	10 (66.7)	3 (50.0)
18 years to <= 21 years	5 (13.9)	3 (20.0)	2 (13.3)	0 (0.0)
Sex (n, %)				
Male	19 (52.8)	9 (60.0)	8 (53.3)	2 (33.3)
Female	17 (47.2)	6 (40.0)	7 (46.7)	4 (66.7)

PK parameters for paediatric and adolescent patients dosed at 92 mg/m^2 BID at C1D1, C1D8 and C3D1 are presented in Table 10 and associated boxplot in Figure 3 and plot in

Figure 4. Tmax was reached at 2h and no difference in plasma exposure was observed across different visits following multiple BID dosing. Compared to C1D1, Cmax accumulation ratio at steady-state was 2.29 and 2.1 at C1D8 and C3D1 respectively.

Figure 3. Boxplot of steady-state PK parameters

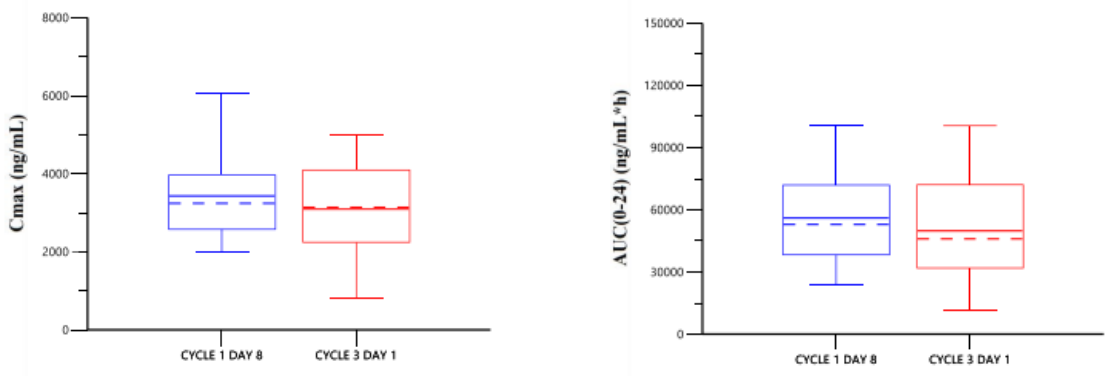


Figure 4. Selpercatinib mean plasma concentration vs time profiles (semilog y) for paediatric and adolescent patients receiving 92 mg/m² BID at C1D1, C1D8 and C3D1

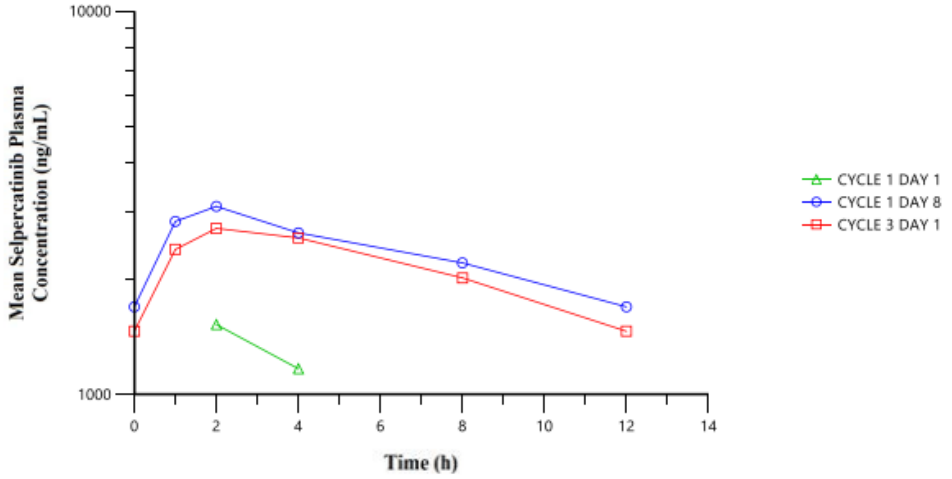


Table 10. PK parameter estimates by Non-compartmental analysis (NCA)

	Geometric Mean (%CV)		
Visit	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 3 Day 1**
Dose	**92 mg/m² BID**	**92 mg/m² BID**	**92 mg/m² BID**
N	35	34	26
C_{max} (ng/mL)	1420 (56)	3290 (30)	2830 (49)
t_{max}[a] (h)	2.03 (1.83-4.35)	2.00 (0.73-7.75)	2.02 (0.78-7.78)
AUC(0-12) (ng/mL*h)	NC	26100 (40)[b]	21700 (62)[c]
AUC(0-24) (ng/mL*h)	NC	52200 (40)[b]	43400 (62)[c]
CL_{ss}/F (L/h)	NC	4.34 (44)[b]	5.64 (63)[c]
$R_A C_{max}$	NC	2.29 (47)	2.10 (58)[c]

Abbreviations: AUC(0-24) = area under the plasma concentration-time curve from time 0 to 24 hours, calculated as 2 x AUC(0-12); AUC(0-12) = area under the plasma concentration-time curve from time 0 to 12 hours; BID = twice daily; CL_{ss}/F = apparent total clearance of drug after oral administration at steady-state; C_{max} = maximum plasma concentration; CV% = percent coefficient of variation; N = number of patients; NC = not calculated; $R_A C_{max}$ = accumulation ratio for C_{max} at steady-state/C_{max} at C1D1; t_{max}= time to reach maximum plasma concentration

[a] Median (minimum-maximum).
[b] N=33.
[c] N=25.

The effects of age, formulation and tumour-type was also investigated and results are presented in Table 11, Table 12 and Table 13, respectively.

Table 11. Selpercatinib PK of paediatric and adolescent patients at 92 mg/m^2 BID at C1D8 by age

	Geometric mean (%CV)				
	Patients ≥2 and <6 yr	**Patients ≥6 and <12 yr**	**Patients ≥12 and <18 yr**	**Patients ≥18 and <21 yr**	**All Patients**
Dose	**92 mg/m^2 BID**	**92 mg/m^2 BID**	**92 mg/m^2 BID**	**92 mg/m^2 BID**	**92 mg/m^2 BID**
N	3	6	20	5	34
Age[a] (y)	5.00 (2.00-5.00)	6.00 (6.00-11.0)	14.0 (12.0-17.0)	20.0 (18.0-20.0)	13.0 (2.00-20.0)
C_{max} (ng/mL)	2300 (8)	3240 (44)	3470 (26)	3340 (31)	3290 (30)
t_{max}[a] (h)	1.08 (0.73-2.00)	1.95 (0.95-4.05)	2.00 (0.92-7.75)	4.00 (1.05-4.12)	2.00 (0.73-7.75)
AUC(0-24) (ng/mL*h)	32300 (21)	48100 (54)	55600[b] (28)	60700 (55)	52200 (40)

Abbreviations: AUC(0-24) = area under the plasma concentration-time curve from time 0 to 24 hours, calculated as 2 x AUC(0-12); BID = twice daily; C_{max} = maximum plasma concentration; %CV = percent coefficient of variation; N = number of participants; t_{max} = time to reach maximum plasma concentration.

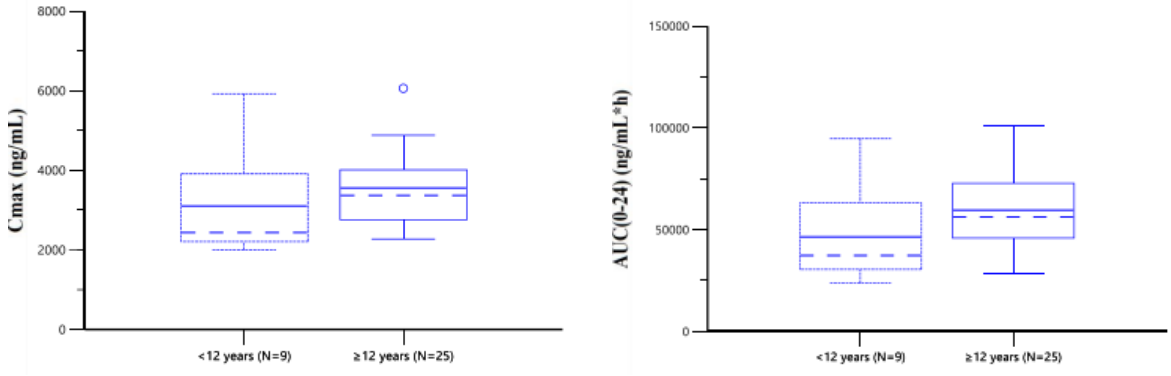
[a] Median (minimum-maximum).

[b] N=19.

The dose of 92 mg/m^2 BID (up to a maximum of 160 mg BID) resulted in a similar steady-state exposure at C1D8 in paediatric and adolescent patients as in adult patients with cancer in LIBRETTO-001 (**JZJA**) treated with 160 mg BID [Cmax geometric mean of 3090 ng/mL (%CV 51, N=683) and AUC(0-24) geometric mean of 53,600 ng/mL*h (%CV 55, (N=667)]. Results are presented for patients aged 2 years and over and less than 6 years, but due to limited data, full conclusions cannot be drawn for this age group.

When the PK parameters were split by age < or > 12 years, the dose of 92 mg/m^2 BID resulted in similar range (overlapped exposure) as shown in Figure 5.

Figure 5. Boxplot of steady-state PK parameters by age group



Limited PK data are available for patients receiving the tablet formulation.

Table 12. Selpercatinib PK of paediatric and adolescent patients at 92 mg/m² BID at C1D8 by formulations

	Geometric Mean (%CV)	
Dose	**92 mg/m² BID**	
Formulation	**Capsule**	**Suspension**
N	27	7
Age[a] (y)	14.0 (5.00-20.0)	6.00 (2.00-15.0)
C_{max} (ng/mL)	3270 (26)	3360 (46)
t_{max}[a] (h)	2.00 (0.92-7.75)	1.03 (0.73-4.05)
AUC(0-24) (ng/mL*h)	54100[b] (35)	45800 (57)

Abbreviations: AUC(0-24) = area under the plasma concentration-time curve from time 0 to 24 hours, calculated as 2 x AUC(0-12); BID = twice daily; C_{max} = maximum plasma concentration; %CV = percent coefficient of variation; N = number of participants; t_{max} = time to reach maximum plasma concentration.

a Median (minimum-maximum)

b N=26

Paediatric Exposure results show that Cmax and AUC24 overlap by tumour type.

Table 13. Selpercatinib PK of paediatric and adolescent patients at 92 mg/m^2 BID at C1D8 by tumour type

	Geometric mean (%CV)			
Dose	**92 mg/ m^2 BID**			
Tumor Type	**Medullary Thyroid**	**Papillary Thyroid**	**Other[a]**	**All Patients**
N	12	15	6	33
Age[b] (y)	15.0 (2.00-20.0)	13.0 (6.00-20.0)	9.50 (5.00-15.0)	13.0 (2.00-20.0)
C_{max} (ng/mL)	2980 (27)	3620 (30)	3120 (39)	3280 (31)
t_{max}[b] (h)	2.00 (0.73-4.17)	2.00 (0.92-4.02)	1.94 (0.95-7.75)	2.00 (0.73-7.75)
AUC(0-24) (ng/mL*h)	45500 (40)	62000[c] (36)	46900 (42)	52400 (41)

Abbreviations: AUC(0-24) = area under the plasma concentration-time curve from time 0 to 24 hours, calculated as 2 x AUC(0-12); BID = twice daily; C_{max} = maximum plasma concentration; %CV = percent coefficient of variation; N = number of participants; t_{max} = time to reach maximum plasma concentration.

[a] Other tumor category includes 3 patients with *RET*-fusion-positive cancer

[b] Median (minimum-maximum).

[c] N=14

In study JZJJ, a palatability and acceptability sub-study was performed for the tablet formulation using a questionnaire. Results from this study were presented for the limited number of patients and caregivers that completed the questionnaire, and answered with satisfactory results.

PK/PD modelling

Population PK analysis

Three different PPK reports were provided dated 22 Nov 2023 (PPK1), 11 Dec 2024 (PPK2) and 12 May 2025 (PPK3), differing by the number of subjects from Study **JZJJ** (LIBRETTO-121). PPK1 include the preliminary PK data from 27 subjects from study **JZJJ** combined to those from the study **JZJA** (LIBRETTO-001). PPK2 was an update of PPK1 with the additional PK data from 9 subjects. PPK3 is the "final report" and include all the subjects from study **JZJJ** (n= 36). In the following, the last report will be presented.

Objectives

The objectives of this analysis was to update a previously PPK1 model for adults and paediatric and adolescent patients with the final paediatric and adolescent data from study **JZJJ**, to perform a covariate analysis on this updated PPK3 model and to perform simulations using the recommended dosing regimen in paediatric and adolescent patients with an activating *RET* alteration and an advanced solid or primary central nervous system tumour.

Methods

The selpercatinib PPK3 model was developed in three steps involving the use of a base model (PPK1), then a search of covariates of interest and finally the selection of the final model.

Covariates of interests were baseline demographic covariates (age, BW, gender and race), dose, hepatic and renal function measurement (liver test function and CLCr), and concomitant medication.

Although age is an important covariate to account for organ maturation, informative data (from neonates or infants) were not available. Mechanistic maturation models for selpercatinib (e.g. the maturation model for CYP3A4) were not tested due to the lack of post-natal age information and data in paediatric population within the age range for maturation.

The final PPK model was evaluated using standard goodness of fit (GOF), visual predictive check and bootstrap.

Simulations were performed using the recommended dosing regimen administered to a virtual population of paediatric and adolescent patients aged 2 to <18 years of age. A therapeutic range for efficacy and safety had not been established for selpercatinib, therefore paediatric posology aimed to match selpercatinib exposure in paediatric and adolescent patients to the exposure observed in adult patients with cancer treated with 160 mg BID. Maximum concentration (Cmax), and area under the curve over two dosing intervals (AUC24) on C1D8 were simulated and summarised for the recommended dosing regimen.

Results

PK dataset

An overview of the different studies and tested dose across the adult, adolescent (**JZJA**, **LIBRETTO-001**) and paediatric and adolescent (**JZJJ**, **LIBRETTO-121**) is provided in Table 14 and Table 15.

Table 14. Summary of study design with selpercatinib

Study number	*Type*	*Subject numbers**	*Treatment regimen(s)*
JZJA	Adult Phase 1/2	793/793	Phase 1 (dose escalation): 20, 40, 60, 80, 120, 160, 200, 240 mg BID, 20 mg QD Phase 2 (dose expansion): 160 mg BID
JZJJ	Paediatric Phase 1/2	36/36	Phase 1 (dose escalation): BID doses of 46 mg/m² (80 mg**), 70 mg/m² (120 mg**), 92 mg/m² (160 mg**), 116 mg/m² (200 mg**), 140 mg/m² (240 mg**) Phase 2 (dose expansion): 92 mg/m² BID (160 mg BID**)

BID: twice daily, QD: once daily.
*total/active population as planned in protocol
** estimated equivalent adult dose (see Table 3-1, Clinical Protocol LOXO-RET-18036 (J2G-OX-JZJJ)

Table 15. Number of patients (%) at each starting dose regimen per study

Covariate	JZJA	JZJJ	Total
Starting dose regimen			
20 mg QD/BID	16 (2.0%)	0 (0.0%)	16 (1.9%)
40 mg BID	16 (2.0%)	2 (5.6%)	18 (2.1%)
60 mg BID	13 (1.6%)	0 (0.0%)	13 (1.5%)
70 mg BID	0 (0.0%)	3 (8.3%)	3 (0.4%)
80 mg BID	19 (2.4%)	5 (13.9%)	24 (2.9%)
100 mg BID	0 (0.0%)	1 (2.8%)	1 (0.1%)
110 mg BID	0 (0.0%)	1 (2.8%)	1 (0.1%)
120 mg BID	21 (2.6%)	8 (22.2%)	29 (3.5%)
140 mg BID	0 (0.0%)	6 (16.7%)	6 (0.7%)
160 mg BID	709 (88.3%)	10 (27.8%)	719 (85.7%)
200 mg BID	3 (0.4%)	0 (0.0%)	3 (0.4%)
240 mg BID	6 (0.7%)	0 (0.0%)	6 (0.7%)

The combined dataset includes evaluable PK data from 839 patients (803 from **JZJA** and 36 from **JZJJ**) with a total of 8123 selpercatinib concentration-time data points (7722 from **JZJA** and 401 from **JZJJ**). A total of 133 concentrations were below the quantification limit (BQL) and excluded. Exploratory plots from study **JZJA** and **JZJJ** are presented in Figure 6 and Figure 7 respectively.

Selpercatinib is expected to reach steady-state by Cycle1 Day8 (C1D8)and the target selpercatinib exposures in adults are defined by Cmax and AUC24 values on C1D8 (see Methods). The plots confirmed adequate compliance with the PK collection schedule in **JZJJ**. Study **JZJJ** contributed only 5% (401 of 8123 observations) of the PK data and most patients received 160 mg BID (88% in **JZJA** and 28% in **JZJJ**). Due to the imbalance in data from paediatric and adolescent patients and adults, the predictive performance for population PK model for the combined **JZJA** and **JZJJ** data focused on the prediction of data collected on C1D8 in **JZJJ**.

Figure 6. Observed concentrations of selpercatinib (JZJA study)

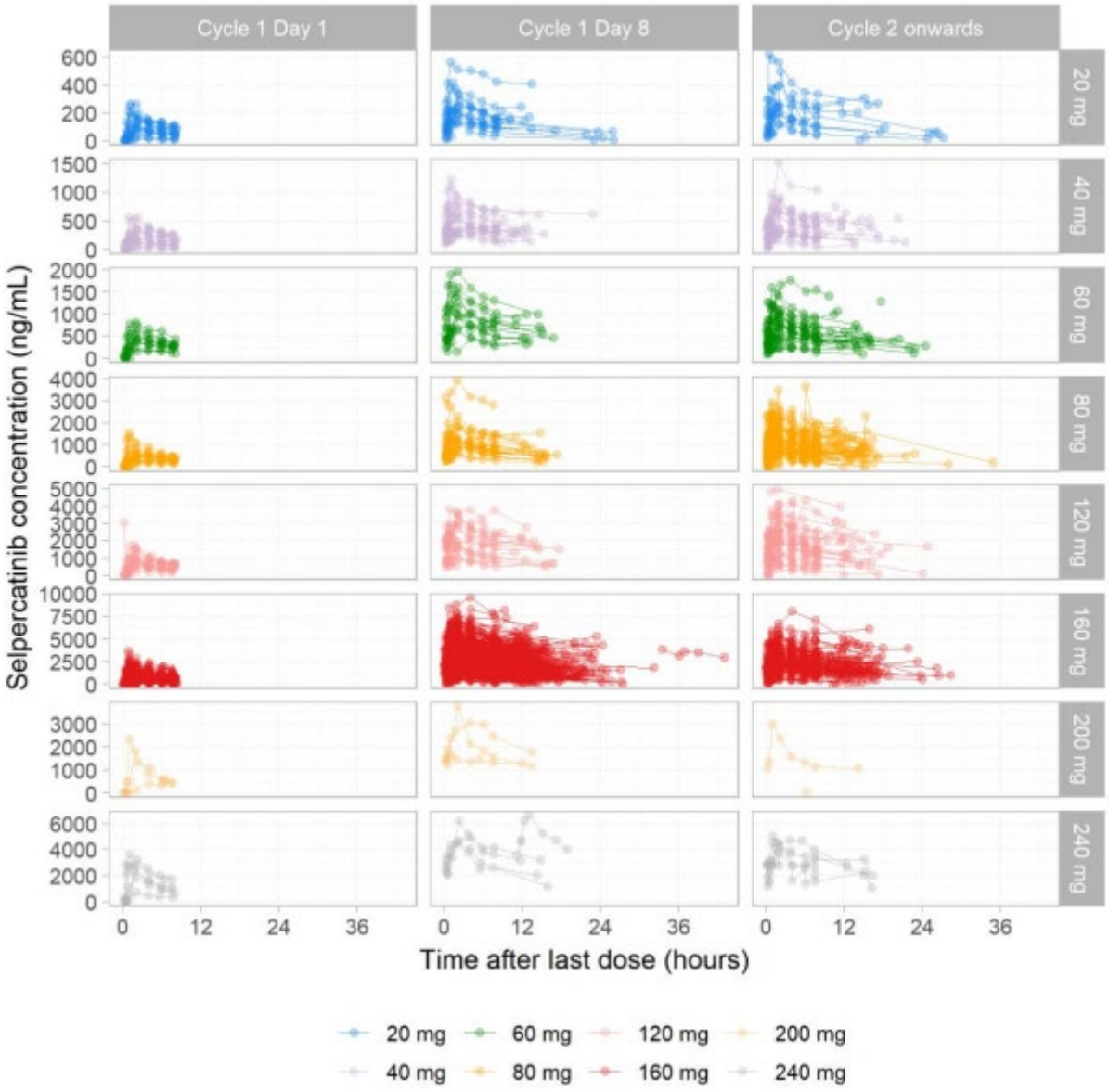
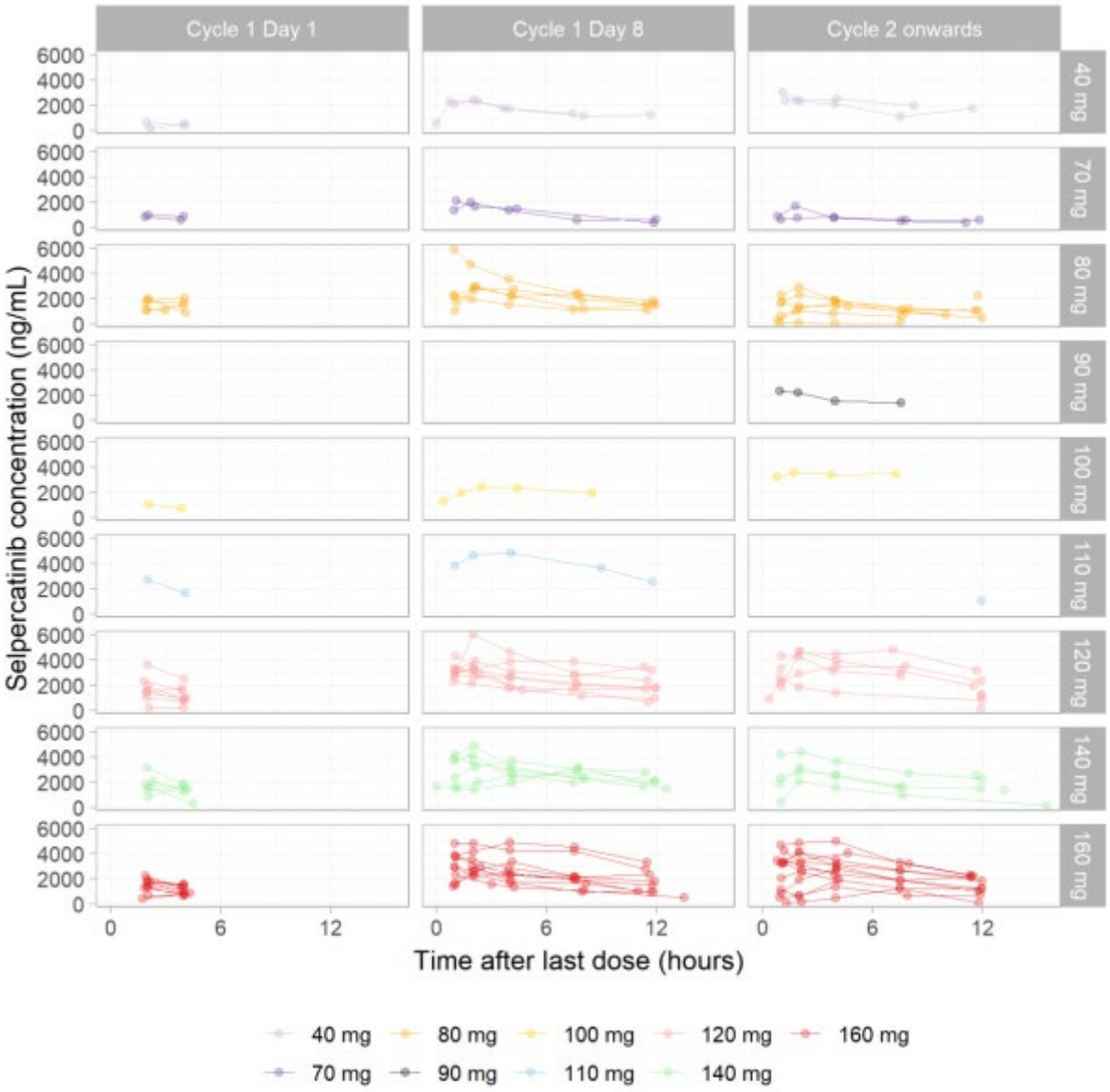


Figure 7. Observed concentrations of selpercatinib (JZJJ study)



A summary of continuous and categorical covariates is presented in Table 16.

Table 16. Summary of covariate information by study

Covariate	JZJA	JZJJ	Total
Sex			
Male	411 (51.2%)	19 (52.8%)	430 (51.3%)
Female	392 (48.8%)	17 (47.2%)	409 (48.7%)
Age (years)	57.4 (14.1)	12.6 (4.76)	55.5 (16.5)
	59.0 [15.0/92.0]	13.0 [2.00/20.0]	58.0 [2.00/92.0]
	[803/0]	[36/0]	[839/0]
Age group			
<12 years	0 (0.0%)	11 (30.6%)	11 (1.3%)
≥12 but <18 years	3 (0.4%)	20 (55.6%)	23 (2.7%)
≥18 years	800 (99.6%)	5 (13.9%)	805 (95.9%)
Weight (kg)	71.0 (19.6)	44.4 (20.8)	69.9 (20.4)
	67.3 [26.8/179]	47.2 [9.60/97.7]	66.5 [9.60/179]
	[803/0]	[36/0]	[839/0]
BSA (m^2)	1.80 (0.258)	1.34 (0.423)	1.78 (0.283)
	1.77 [1.11/2.79]	1.43 [0.446/2.21]	1.76 [0.446/2.79]
	[803/22]	[36/0]	[839/22]
AST (U/L)	28.0 (19.5)	27.4 (13.8)	27.9 (19.3)
	23.0 [6.00/233]	22.5 [13.0/86.0]	23.0 [6.00/233]
	[803/0]	[36/0]	[839/0]
ALT (U/L)	25.3 (18.5)	18.0 (8.68)	25.0 (18.2)
	20.0 [4.00/158]	15.0 [5.00/37.0]	19.0 [4.00/158]
	[803/0]	[36/0]	[839/0]
Total bilirubin	9.86 (5.71)	8.80 (4.33)	9.81 (5.66)
(µmol/L)	8.55 [2.50/56.4]	8.55 [1.00/18.8]	8.55 [1.00/56.4]
	[803/0]	[36/0]	[839/0]
Creatinine clearance	97.5 (45.3)	146 (48.1)	99.6 (46.5)
(mL/min)	91.0 [20.7/762]	137 [88.5/310]	92.9 [20.7/762]
	[803/0]	[36/0]	[839/0]
Race			
White	543 (67.6%)	17 (47.2%)	560 (66.7%)
Black or African American	26 (3.2%)	3 (8.3%)	29 (3.5%)
Asian	193 (24.0%)	10 (27.8%)	203 (24.2%)
American Indian or Alaska Native	2 (0.2%)	0 (0.0%)	2 (0.2%)
Native Hawaiian or Other Pacific Islander	1 (0.1%)	0 (0.0%)	1 (0.1%)
Other	32 (4.0%)	4 (11.1%)	36 (4.3%)
Unknown/Missing	6 (0.7%)	2 (5.6%)	8 (1.0%)

Covariate	JZJA	JZJJ	Total
Any CYP3A4 inhibitors			
No	529 (65.9%)	36 (100.0%)	565 (67.3%)
Yes	274 (34.1%)	0 (0.0%)	274 (32.7%)
Strong CYP3A4 inhibitors			
No	774 (96.4%)	36 (100.0%)	810 (96.5%)
Yes	29 (3.6%)	0 (0.0%)	29 (3.5%)
Moderate CYP3A4 inhibitors			
No	656 (81.7%)	36 (100.0%)	692 (82.5%)
Yes	147 (18.3%)	0 (0.0%)	147 (17.5%)
Weak CYP3A4 inhibitors			
No	646 (80.4%)	36 (100.0%)	682 (81.3%)
Yes	157 (19.6%)	0 (0.0%)	157 (18.7%)
Any CYP3A4 inducers			
Missing	803 (100.0%)	36 (100.0%)	839 (100.0%)
Strong CYP3A4 inducers			
Missing	803 (100.0%)	36 (100.0%)	839 (100.0%)
Moderate CYP3A4 inducers			
Missing	803 (100.0%)	36 (100.0%)	839 (100.0%)
Weak CYP3A4 inducers			
Missing	803 (100.0%)	36 (100.0%)	839 (100.0%)
H2-blockers			
No	504 (62.8%)	35 (97.2%)	539 (64.2%)
Yes	299 (37.2%)	1 (2.8%)	300 (35.8%)
PPIs			
No	653 (81.3%)	36 (100.0%)	689 (82.1%)
Yes	150 (18.7%)	0 (0.0%)	150 (17.9%)
PPIs or H2-blockers			
No	437 (54.4%)	35 (97.2%)	472 (56.3%)
Yes	366 (45.6%)	1 (2.8%)	367 (43.7%)

Continuous values are shown as mean (standard deviation) median [range] [sample size/number missing]. Values were rounded to 3 significant digits. Categorical values are shown as number of subjects (%). ALT: alanine aminotransferase, AST: aspartate aminotransferase. BSA: body surface area.
Categorical values are shown as number of subjects (%).
H2-blocker: H2 receptor antagonists, PPIs: proton pump inhibitor

Final PPK model

Figure 8, Figure 9 and Figure 10 provides the associated GOF and pcVPC using the final PK model. Standard GOF plots demonstrate the absence of systematic model misspecification and this is confirmed in the CWRESI vs TAD. In the pcVPC plots, and particularly for C1D8, the central tendency in the data was well captured by simulated data for JZJJ. Importantly for C1D8 the 2.5th and 97.5th percentiles of the observed data were within the 95% CI of the simulated data.

Eta-shrinkage was high >30% except for CL/F (3.5%).

A total of 400 bootstrapped data sets were generated and were considered sufficient to compute standard errors for all parameters (11 runs terminated and 2 near boundary were not included).

Figure 8. GOF plots for the combined dataset (left) or for study JZJJ (right)

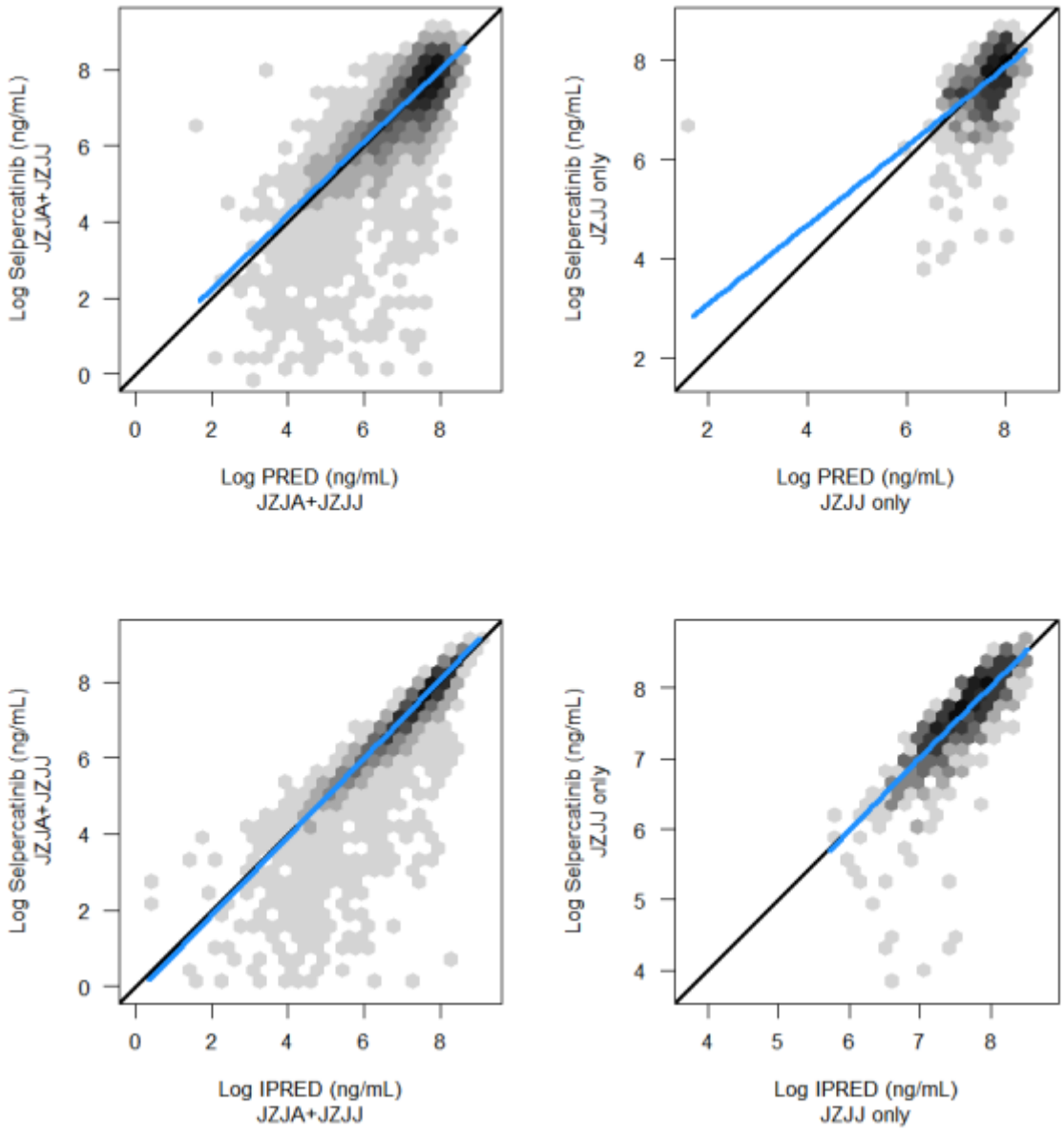


Figure 9. GOF plots by using CWRES for the combined dataset (left) or for study JZJJ (right)

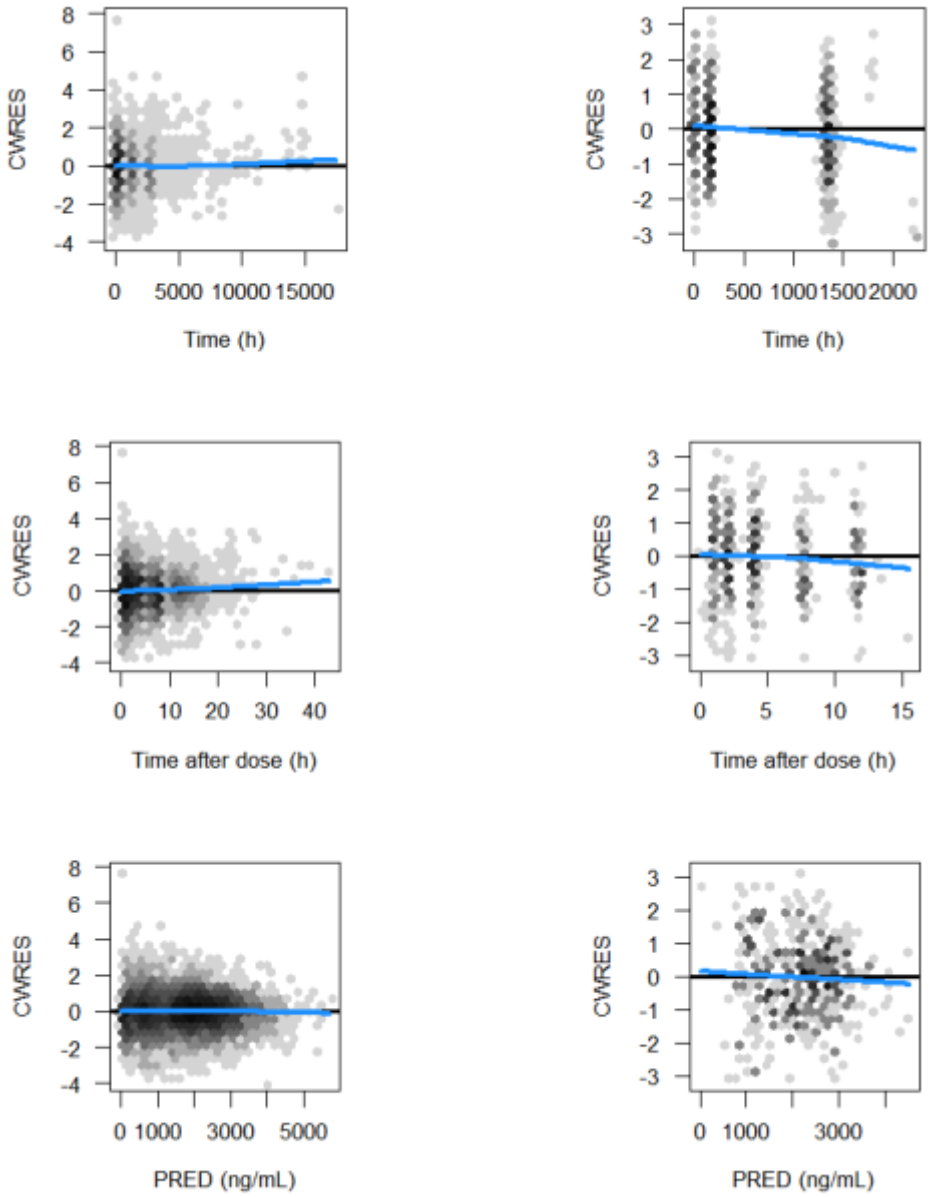
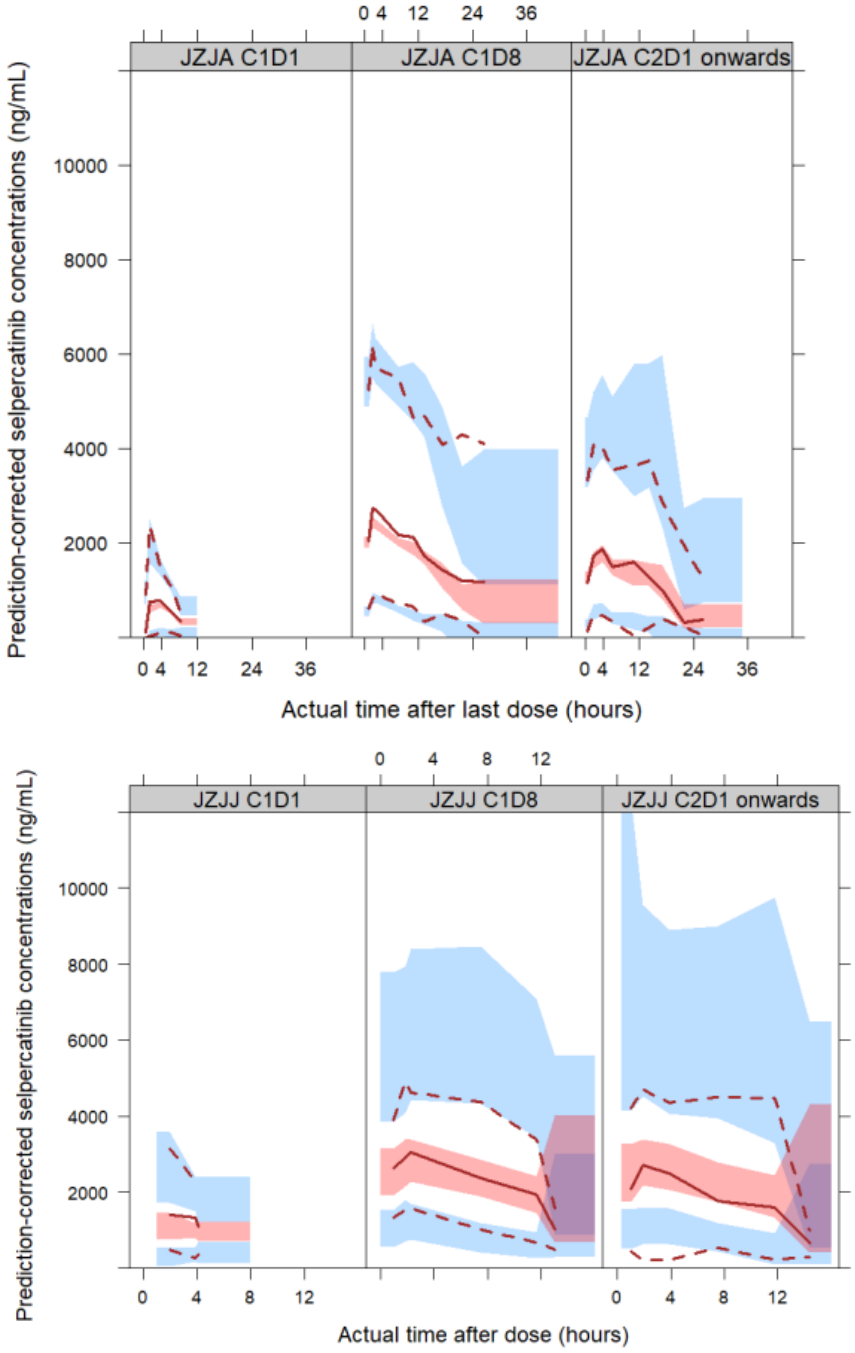


Figure 10. pcVPC by period of observations and by study JZJA (up) and JZJJ (down)



Simulations

The final model (run204) was used to perform simulations to compare selpercatinib exposure (Cmax and AUC24 on C1D8) in paediatric and adolescent patients aged 2 to <18 years of age with selpercatinib exposure in adult patients with cancer treated with 160 mg BID. The exposure metrics are presented using mg/L instead of ng/mL.

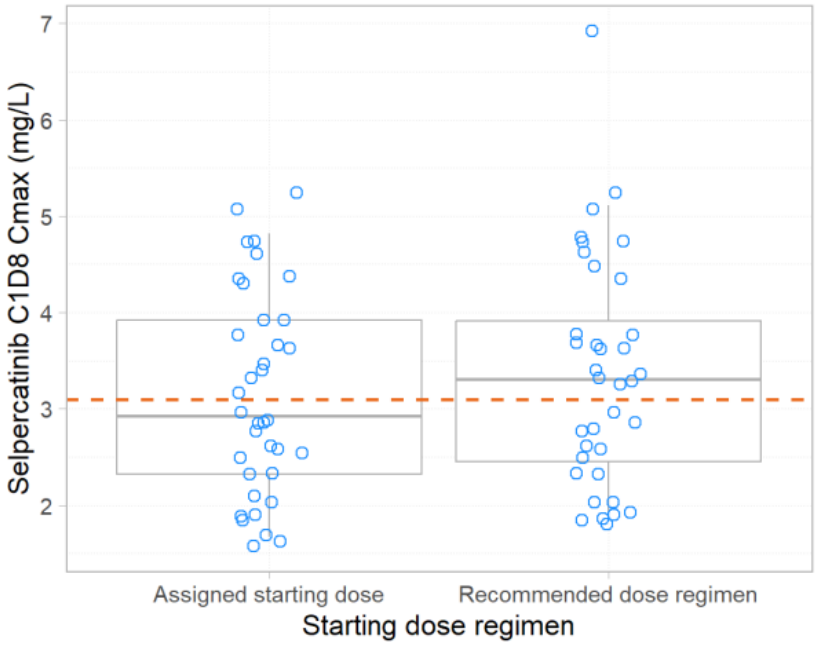
The simulated C1D8 Cmax and AUC24 on C1D8 for patients in study JZJJ using the actual starting dose and the recommended dosing regimen are summarised in Table 17 and compared with exposure observed in adult patients with cancer treated with 160 mg BID (AUC24 of 53.6 mg*h/L and Cmax of 3.09 mg/L) in Figure 11 (C1D8 Cmax and AUC24).

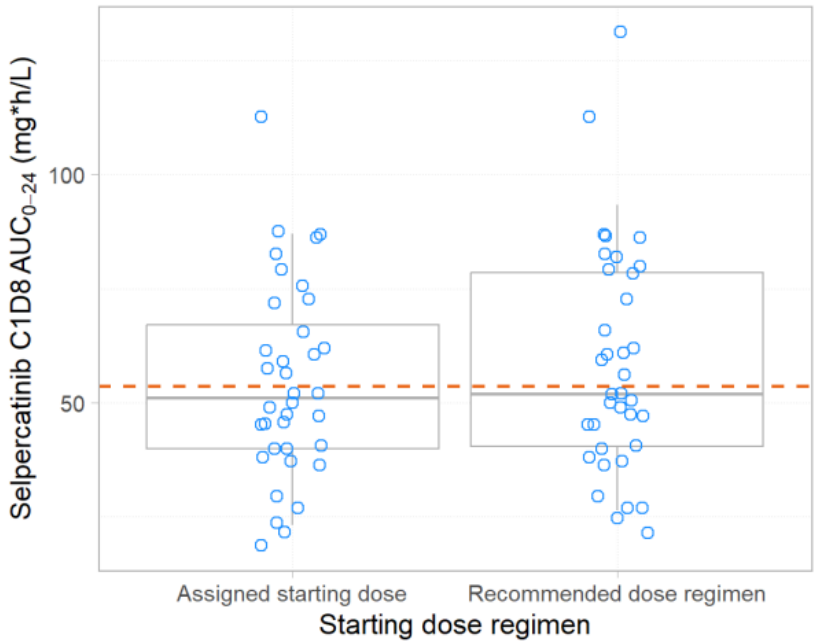
Table 17. Summary of simulated PK parameter by dosing regimen in JZJJ on C1D8

Exposure metric	Assigned starting dose	Recommended dose regimen
Cmax (mg/L)	3.15 (1.06) 2.92 [1.58/5.24] [36/0]	3.35 (1.19) 3.30 [1.80/6.92] [36/0]
AUCss (mg*h/L)	54.6 (21.4) 51.0 [18.8/113] [36/0]	58.4 (24.8) 51.9 [21.5/131] [36/0]

Continuous values are shown as mean (standard deviation) median [range] [sample size/number missing]. Values were rounded to 3 significant digits.
AUCss: area under the concentration versus time curve at steady state, Cmax: maximum concentration.

Figure 11. Boxplot of simulated selpercatinib Cmax (up) and AUC24 (down) at C1D8 using the started and the recommended dose regimen compared to the adult targets (dot line) from JZJA





Simulations using the NHANES DXA database for patients 6 months to < 18 years were performed. Data from 10911 individuals from the NHANES DXA database was used to provide linked demographic variables of age, height, and weight to simulate selpercatinib concentration-time data for paediatric and adolescent patients for ages 2 years to > 18 years. The NHANES database did not include race information, and all individuals were classified as not Asian for the simulations. The covariate relationships of dose with clearance, and body weight with clearance and volume parameters (using standard allometry) were included.

The simulated selpercatinib exposure on C1D8 for the paediatric patients from the NHANES DXA database are summarized by age categories (Table 18) and by weight categories (

Table 19). Associated plots are presented in Figure 12 and Figure 13 respectively. For BSA categories associated box plots are presented in Figure 14.

Table 18. Simulated PK parameters by age group with the recommended dosing regimen

Exposure metric	2 ≤ age <6 years	6 ≤ age < 12 years	12 ≤ age < 18 years	age ≥ 18 years
Cmax (mg/L)	3.59 (1.71) 3.26 [0.731/17.2] [2439/0]	3.28 (1.46) 3.02 [0.715/15.1] [3203/0]	3.27 (1.50) 2.96 [0.587/13.2] [5242/0]	2.91 (1.37) 2.63 [0.418/14.5] [14941/0]
AUCss (mg*h/L)	60.9 (34.6) 53.3 [9.80/309] [2439/0]	58.6 (31.6) 52.2 [5.65/342] [3203/0]	61.5 (32.7) 54.3 [9.60/309] [5242/0]	55.2 (30.2) 48.5 [7.10/341] [14941/0]

Figure 12. Simulated selpercatinib Cmax (up) and AUC24h (down) at C1D8, by age group with the recommended dosing regimen

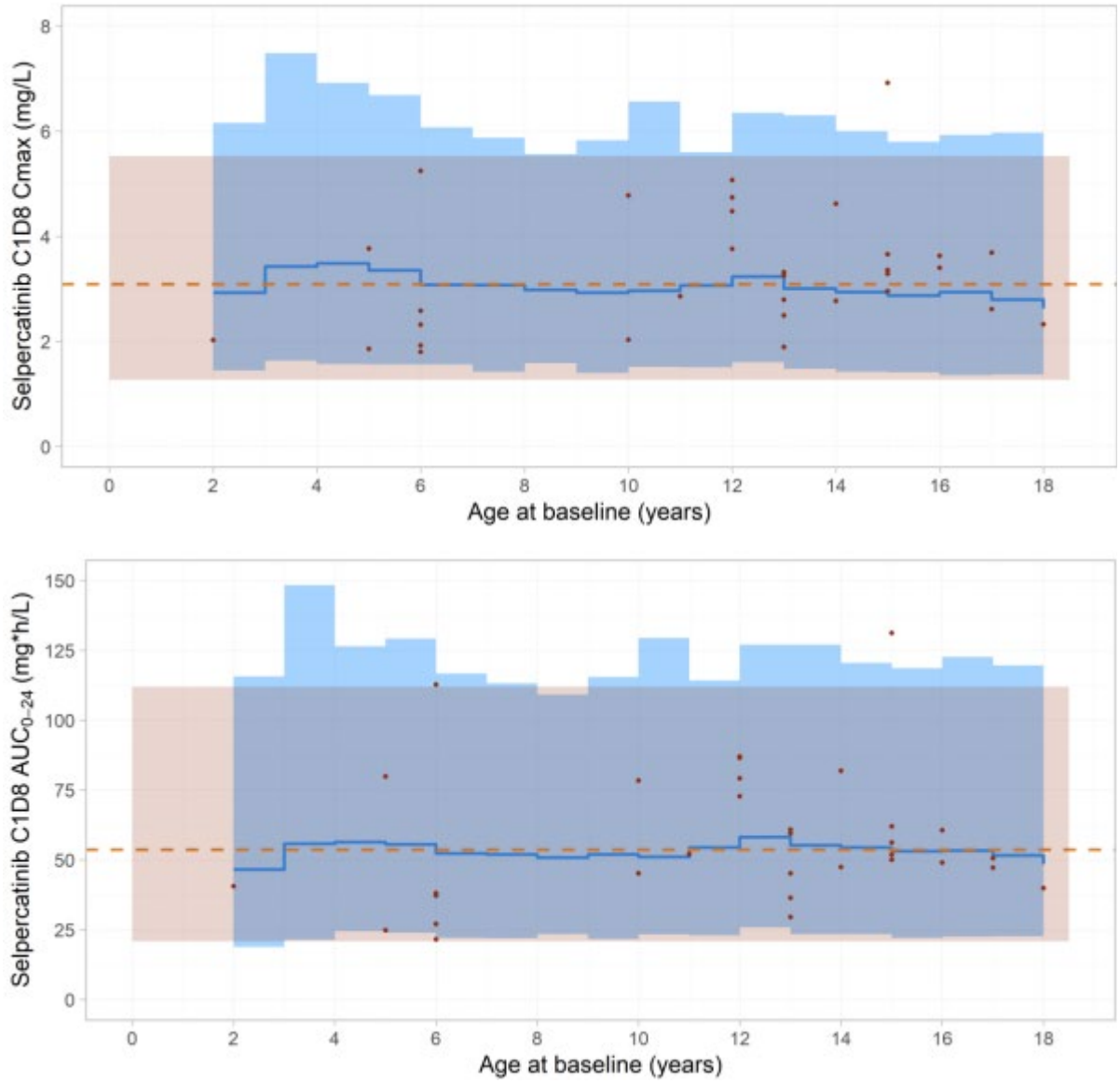


Table 19. Simulated PK parameters by BW/BSA group with the recommended dosing regimen

Exposure metric	0.33 ≤ BSA ≤ 0.65 m²	0.65 < BSA ≤ 1.08 m²	1.09 < BSA ≤ 1.52 m²	BSA ≥ 1.53 m²	≥ 12 years and <50 kg	≥ 12 years and ≥ 50 kg
Cmax (mg/L)	3.05 (1.38)	3.56 (1.67)	3.39 (1.48)	3.33 (1.56)	3.26 (1.43)	2.98 (1.41)
	2.77	3.25	3.14	2.98	2.97	2.69
	[0.731/9.55]	[0.715/17.2]	[0.800/15.1]	[0.754/9.52]	[0.711/11.5]	[0.418/14.5]
	[983/0]	[2987/0]	[1414/0]	[258/0]	[1607/0]	[18576/0]
AUCss (mg*h/L)	51.2 (29.1)	61.2 (33.9)	61.7 (32.2)	62.7 (34.2)	59.5 (31.1)	56.6 (31.0)
	44.0	54.0	55.4	55.3	52.7	49.7
	[9.80/209]	[5.65/309]	[10.0/342]	[13.7/225]	[8.58/268]	[7.10/341]
	[983/0]	[2987/0]	[1414/0]	[258/0]	[1607/0]	[18576/0]

Figure 13. Simulated selpercatinib Cmax (up) and AUC24h (down) at C1D8, by BW group with the recommended dosing regimen

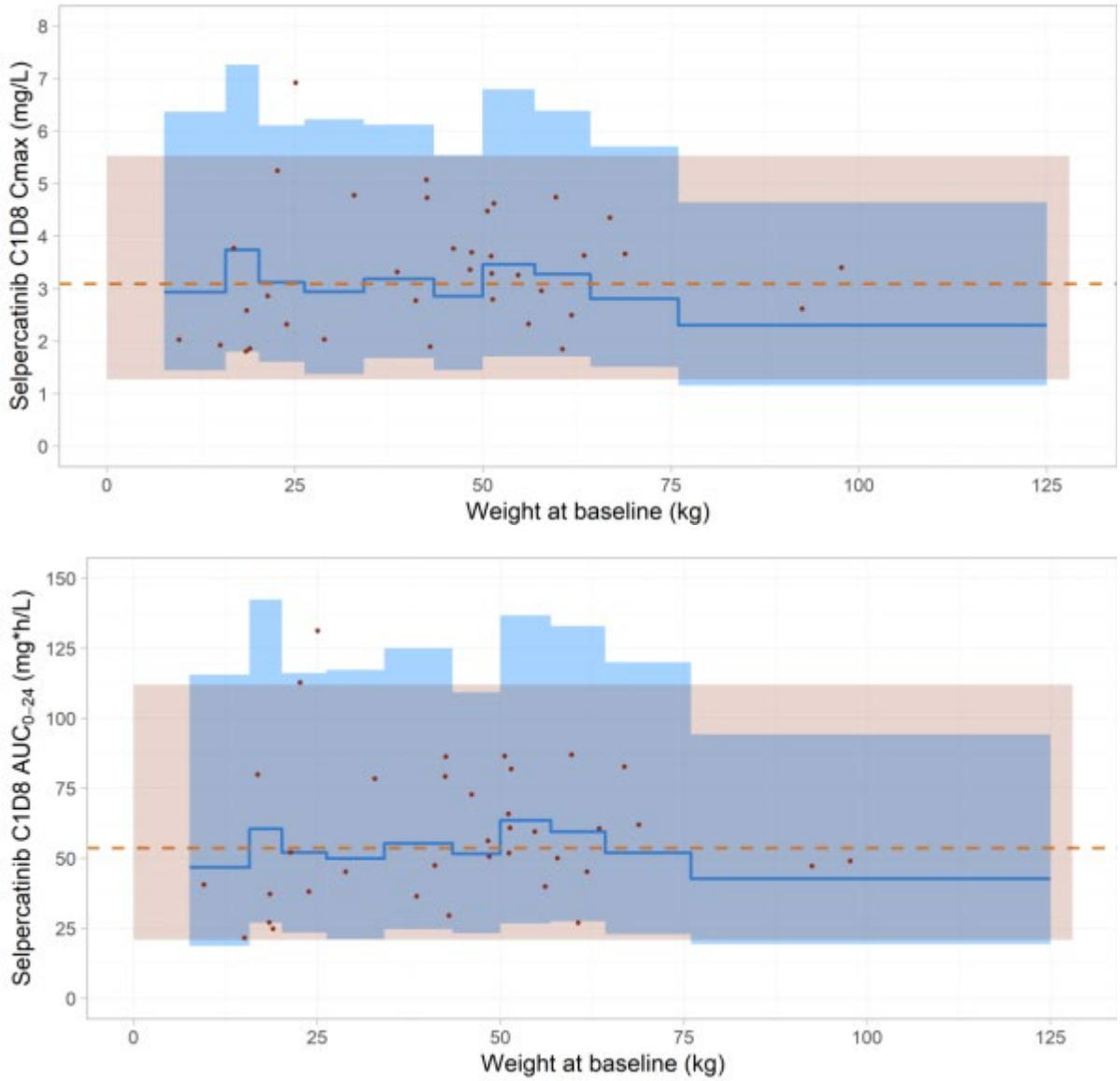
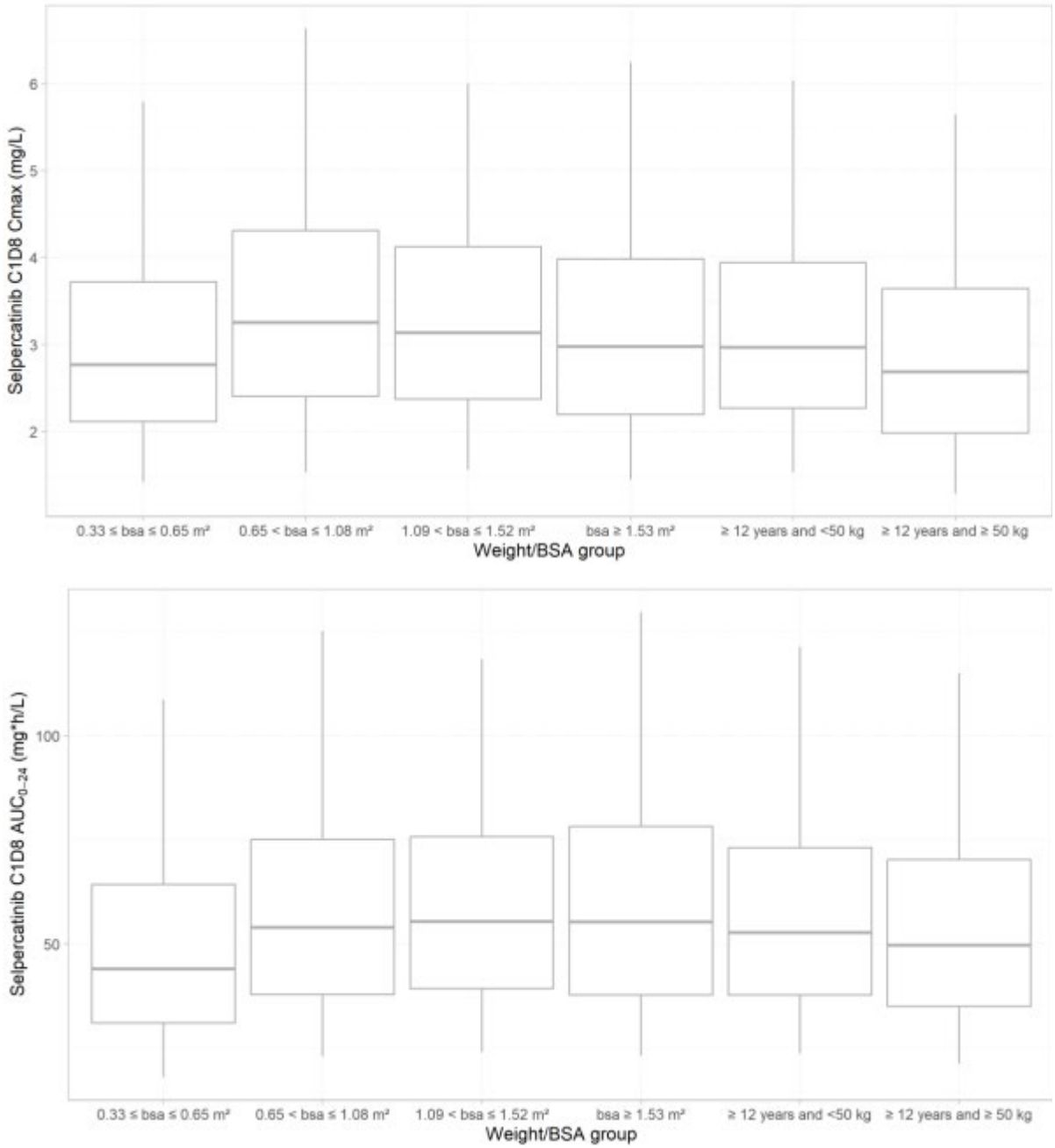


Figure 14. Boxplot of simulated selpercatinib Cmax (up) and AUC24h (down) at C1D8, by BSA/BW group with the recommended dosing regimen



Additional simulations

Simulations were performed using the proposed dosing regimen administered to a virtual population of paediatric and adolescent patients aged 2 to <18 years of age. Two dosing regimens were compared for the lowest BSA cohort (0.45-0.65 m2): 40 mg TID vs 40 mg BID.

Results are provided below in Figure 15 and Figure 16 for the 40 mg BID vs TID dosing regimen for C1D8 Cmax and C1D8 AUC24h, respectively.

Figure 15. Simulated selpercatinib C1D8 Cmax vs BSA for children aged 2 to <12 years from the NHAES database administered BSA dosing (40 mg TID for the lowest BSA 0.45-0.65 m^2, top; and 40 mg BID, bottom)

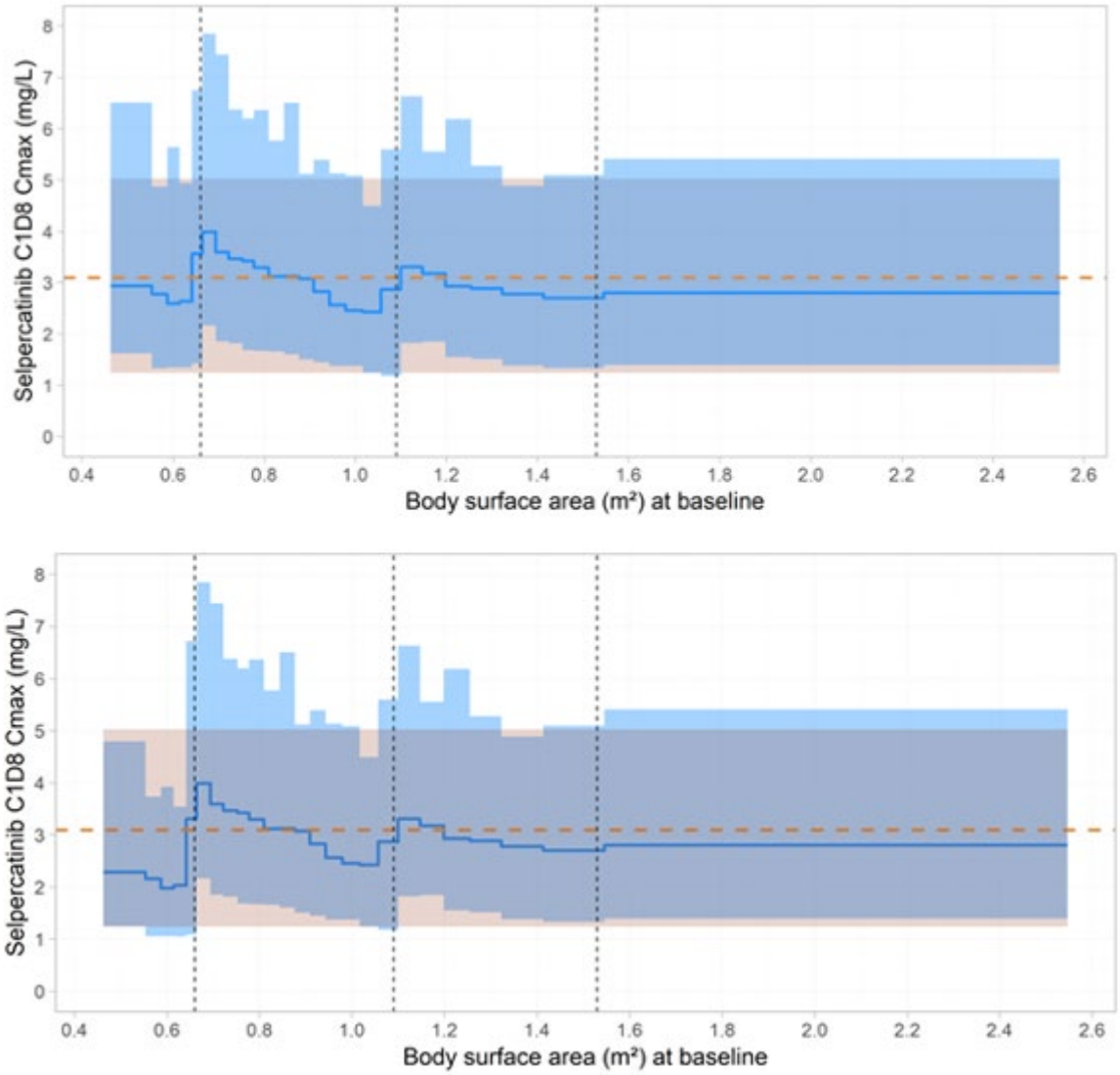
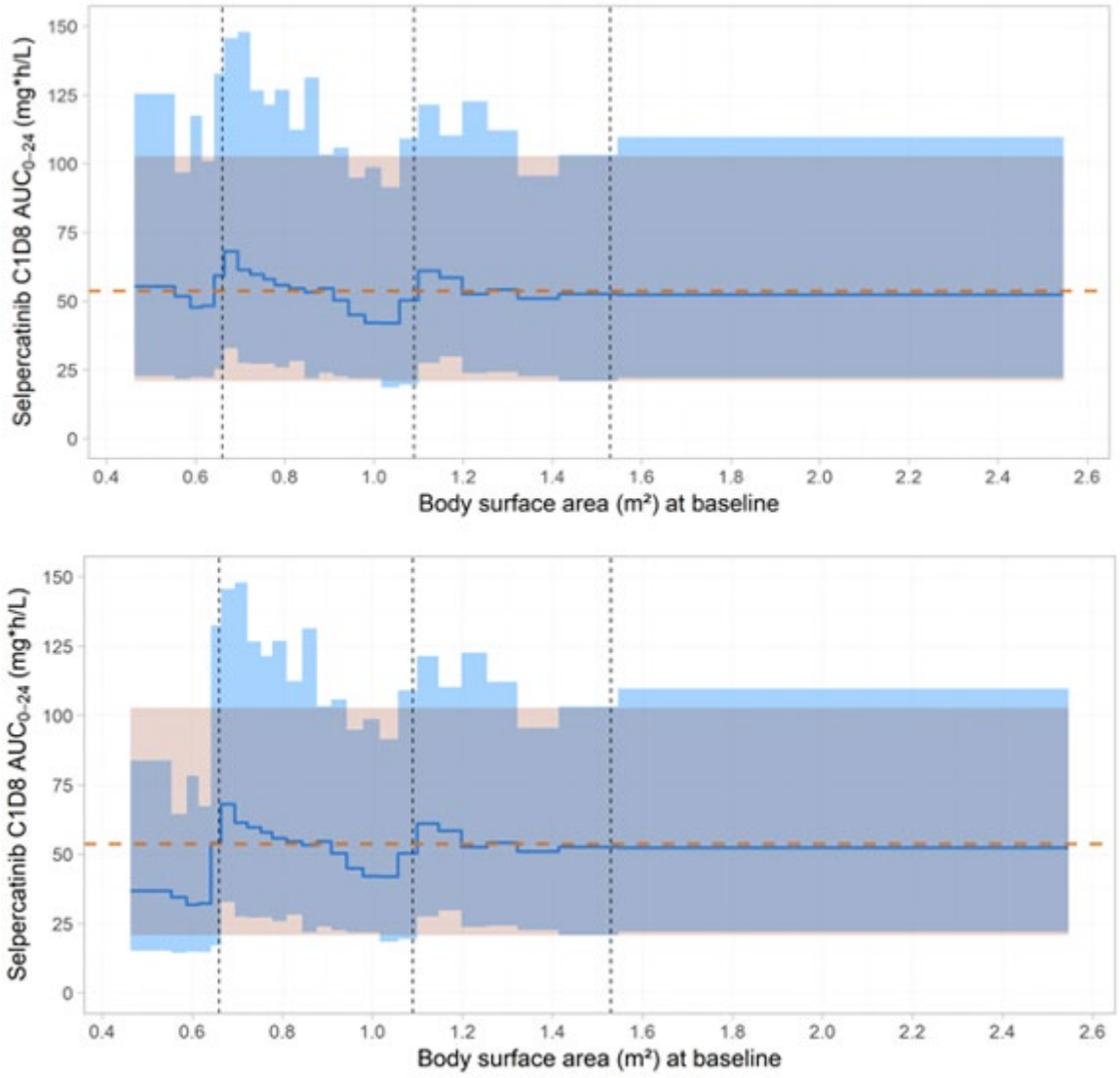


Figure 16. Simulated selpercatinib C1D8 AUC24h vs BSA for children aged 2 to <12 years from the NHAES database administered BSA dosing (40 mg TID for the lowest BSA 0.45-0.65 m^2, top; and 40 mg BID, bottom)



2.4.1.2. PK interaction studies

Study JZPB (J2G-MC-JZPB) was a Phase 1, open-label, fixed sequence, drug interaction study to investigate the effect of a single dose of selpercatinib on the PK of rosuvastatin in healthy participants.

A total of 28 participants were enrolled in the study, of whom 26 received all planned treatments and completed the study.

PK data from one participant were excluded from the analysis of rosuvastatin 20 mg monotherapy due to vomiting occurring within two times the median time to maximum plasma concentration (tmax) of rosuvastatin.

Eligible participants were healthy Caucasian males and females between 18 and 65 years of age. Participants were excluded if they carried the ABCG2 (human breast cancer resistance protein [BCRP] transporter) genotypes c.34AA, c.421AA, or c.34GA/421CA.

On Day 1, participants received a single oral dose of rosuvastatin 20 mg. On Day 5, participants received concurrent oral doses of rosuvastatin 20 mg and selpercatinib 160 mg. An overnight fast of at least 8 hours was required prior to dosing on both study days.

The total study duration for each participant, from the beginning of the screening period through follow-up, was approximately 8 weeks.

The incidence of all treatment-emergent adverse events (TEAEs) reported during the study was similar between the study interventions.

Four participants (14.3%) reported at least 1 TEAE following administration of 20 mg rosuvastatin alone; 3 participants (10.7%) reported at least 1 TEAE following co-administration of 20 mg rosuvastatin and 160 mg selpercatinib. All TEAEs were mild in severity.

No deaths, serious adverse events (SAEs), or discontinuations due to an adverse event (AE) occurred during the study.

Median rosuvastatin tmax was similar when administered alone (4 hours) and when co-administered with selpercatinib (5 hours). Mean rosuvastatin half-life (t1/2) was also similar (23.5 hours versus 19.2 hours when administered alone and with selpercatinib, respectively).

Compared to when 20 mg rosuvastatin was administered alone, coadministration of 20 mg rosuvastatin with 160 mg selpercatinib resulted in a(n):

80% increase in geometric least squares (LS) mean rosuvastatin area under the drug plasma concentration versus time curve from time zero to infinity (AUC[0-∞])(90% confidence interval (CI): 56% to 107%), 71% increase in geometric LS mean rosuvastatin maximum concentration (Cmax) (90% CI: 50% to 95%), and median 0.25 hour increase in rosuvastatin tmax (90% CI: 0 to 0.75 hours).

Between-subject variability (geometric mean coefficient of variation) for rosuvastatin AUC(0-∞), and Cmax was 46.7% and 37.2%, respectively.

After coadministration of 20 mg rosuvastatin with 160 mg selpercatinib, the geometric mean selpercatinib Cmax was 1330 ng/ml (73% coefficient of variation [CV]) and the median tmax was 1.52 hours (range 1 to 6 hours).

In conclusion, following co-administration of 20 mg rosuvastatin with 160 mg selpercatinib, the systemic exposure to rosuvastatin increased by approximately 80% for AUC and 71% for Cmax. Selpercatinib had no effect on the elimination of rosuvastatin, with mean rosuvastatin t1/2 values being similar in the presence and absence of selpercatinib.

Single doses of 160 mg selpercatinib were well-tolerated with respect to AEs when co-administered with 20 mg rosuvastatin and there were generally no clinically meaningful safety findings in terms of vital signs, electrocardiograms (ECGs), and clinical laboratory findings.

2.4.1.3. Discussion on clinical pharmacology

With the current application the MAH is seeking an approval to extend the indications of *RET* fusion-positive TC, *RET*-mutant MTC and *RET* fusion-positive solid tumours of selpercatinib to paediatric patients 2 years of age and older. The commercial formulations planned to be used are the capsule (40 mg and 80 mg) and the tablet (40, 80, 120 and 160 mg) formulations.

In support of this application, a rBA study **JZJU**, a Phase 1/2 study **JZJJ** in the target population and an updated PPK model were provided. The paediatric development is covered by EMEA-002544-PIP01-18-M02.

According to EMEA-002544-PIP01-18-M02, the subset of the paediatric population concerned by the paediatric development was from 6 months to less than 18 years. A development of an age-appropriate tablets and alternative administration instruction and generation of data on acceptability and palatability were planned.

In study **JZJJ** paediatric and adolescent patients aged 2 to <21 years received selpercatinib at a 92 mg/m^2 BID (max: 160 mg BID) dose with either one of the three following formulations (PFOS, capsule or tablet).

Formulations

PK bridging between PFOS 20 mg vs capsule (20 mg) was performed in study **JZJU** and showed that both formulations are BE. Geomean ratio [90%CI] of Cmax, AUCt were 1.04 [0.968-1.11] and 1.02 [0.982-1.06], respectively, both contained within the BE limits [0.8-1.25]. PK bridging between capsule 20 mg vs 40 or 80 mg was discussed with the initial MA. The assessment of the PK bridging between capsule 80 mg (2x80mg) vs tablet 160 mg has been completed in the context of procedure EMEA/H/C/005373/X/0031.

As part of **JZJJ**, an acceptability and palatability study was performed to investigate the use of the tablet as "swallowed intact" or as "swallowed as a dispersion"; participants had to fill in a questionnaire. The tablet dispersion was initially proposed as an alternative for subjects unable to swallow the intact tablet formulation (see also Quality section).

Initially, the inclusion of a reference to the alternative method of administration was proposed for sections 4.2 and 6.6 of the SmPC. However, the bioequivalence of this alternative method-administration was not sufficiently justified. Ultimately, instructions for an alternative administration dosing were not included in the SmPC.

PK results

Based on NCA at C1D8 (at steady-state), the dose of 92 mg/m^2 BID (up to a maximum of 160 mg BID) resulted in a similar steady-state exposure at C1D8 in paediatric and adolescent patients as in adult patients with cancer in LIBRETTO-001 (**JZJA**) treated with 160 mg BID [Cmax geometric mean of 3090 ng/mL (%CV 51, N=683) and AUC(0-24) geometric mean of 53,600 ng/mL*h (%CV 55, (N=667)]. For children aged ≥2 to <6 years geomean Cmax and AUC24h were decreased by approximately 30%. No formulation (PFOS vs Capsule or Tablet vs capsule), nor tumour type effect on selpercatinib PK parameters was observed.

Population PK analysis

The Population PK analysis used PK data from study LIBRETTO-001 (JZJA) and LIBRETTO-121 (JZJJ).

GOF plots did not show any particular misspecification in both studies. Importantly for JZJJ at C1D8 the predictive performance showed an acceptable description of the observed data. The main output of this analysis was used to select fixed dose of selpercatinib within BSA categories from 0.33 to >1.53 m^2 for children aged 2 to<12 years. Initially, this BSA range (0.33 to >1.53 m^2) was proposed for inclusion in section 4.2 of the SmPC. However, this range was not supported by the available demographic data, as no subjects with a BSA <0.45 m^2 were included in study JZJJ. Consequently, no PK data were available to substantiate dose recommendations for subjects with a BSA between 0.33 and 0.45 m^2. Furthermore, the Population PK model used to derive the fixed-dose regimen did not incorporate any maturation function for CYP3A4 clearance, as no data in children below 2 years of age or within the age range relevant for maturation were available. Consequently, the model cannot be expected to reliably predict exposure in patients <2 years or in those with a BSA <0.45 m².

Moreover, the claimed dose of a 40 mg TID in children with a BSA of 0.33 to 0.65 m^2 was never clinically tested. The applicant provided simulations data (Figure 15 and Figure 16) which showed a better matching exposure on adult targets compared to a 40 mg BID dosing regimen, and therefore a 40 mg TID regimen was agreed for the range BSA range of 0.45 to 0.65 m^2. In conclusion, the recommended dose for paediatric patients 2 to less than 12 years of age by BSA, as reflected in the section 4.2 of the SmPC is:

Body surface area (BSA)	**Recommended dose**
0.45 to 0.65 m^2	40 mg three times daily
0.66 to 1.08 m^2	80 mg twice daily
1.09 to 1.52 m^2	120 mg twice daily
≥1.53 m^2	160 mg twice daily

Retsevmo is not recommended for paediatric patients with body surface area less than 0.45 m^2.

PK interaction studies

As selpercatinib was identified as an *in vitro* inhibitor of BCRP, the applicant conducted a dedicated clinical DDI study to evaluate its effect on the pharmacokinetics of rosuvastatin, a sensitive BCRP substrate. In this study, 28 healthy participants received a single dose of rosuvastatin (20 mg) co-administered with selpercatinib (160 mg).

The results demonstrated an increase in rosuvastatin exposure of approximately 80% for AUC and 71% for Cmax in the presence of selpercatinib. Elimination half-life of rosuvastatin (t1/2) was unaffected, indicating that the observed effect is attributable to inhibition of intestinal BCRP rather than changes in systemic elimination.

Overall, while the magnitude of interaction is moderate, it does not warrant a dose adjustment of rosuvastatin when co-administered with selpercatinib. Nevertheless, given the observed increase in systemic exposure, a precautionary statement regarding co-administration with BCRP substrates has been appropriately included in section 4.5 of the SmPC.

2.4.1.4. Conclusions on clinical pharmacology

Overall, the PK of selpercatinib has been sufficiently characterised in paediatric patients aged 2 to <12 years and the recommended fixed dose within a BSA category is supported.

2.4.2. Clinical efficacy

2.4.2.1. Main study(ies)

LIBRETTO-121 (LOXO-RET-18036; J2G-OX-JZJJ)

A Phase 1/2 Study of the Oral RET Inhibitor LOXO 292 in Pediatric Patients with Advanced RET-Altered Solid or Primary Central Nervous System Tumours.

Study Period

Study initiation date: 13 June 2019 (first patient first visit)

End date: 08 November 2024 (data cutoff date for the final clinical study report)

Methods

LIBRETTO-121 is an international multicenter, open-label, single-arm Phase 1/2 study in paediatric and young adult patients aged at least 2 years old patients with advanced solid or primary CNS tumours harbouring an activating *RET* alteration.

The study includes 2 parts:

- Phase 1 (dose escalation), and
- Phase 2 (dose expansion).

This is a Phase 1/2 open-label single arm study. Although we acknowledged the low incidence of the conditions, such a design remains exploratory.

Initially patients from 6 months were to be included however due to the difficulty to enrol very young patients, the lower age was modified to 2 years following PDCO recommendation.

Study participants

Main selection criteria are summarised below.

Inclusion criteria

- Patients at least 6 months of age and 21 years of age or below at Cycle 1 Day 1 with a locally advanced or metastatic solid or primary central nervous system tumour that had relapsed, progressed, or was nonresponsive to available therapies and/or for which no standard or available systemic curative therapy exists.
- Patients who had evidence of an activating *RET* gene alteration in tumour and/or blood (for example, gene rearrangement and/or mutation, excluding synonymous, frameshift, or nonsense mutations) as identified through molecular assays, as performed for clinical evaluation.
- Patients who had measurable or non-measurable but evaluable disease.
- Patients who had a Karnofsky (patients aged 16 years and older) or Lansky (patients younger than age 16 years) performance score of at least 50.

Main exclusion criteria

- Patients who underwent major surgery within 2 weeks prior to C1D1, and/or
- Patients who had active or prior history of events that might put patients at increased risk when taking selpercatinib, such as
    - known cardiac disease
    - uncontrolled infection
    - malabsorption syndrome or gastrointestinal absorption of the drug
    - uncontrolled hypotension or hypertension
    - uncontrolled symptomatic hypothyroidism or hyperthyroidism
    - uncontrolled symptomatic hyperglycaemia or hypocalcaemia, or
    - hypersensitive to any of the components of the investigational agent, selpercatinib or Ora-Sweet® SF and OraPlus®

Four participant cohorts were enrolled (Table 20).

Table 20. Disease Criteria for Enrollment: Cohorts 1 to 4

Cohort	Disease Criteria
Cohort 1	*RET*-fusion-positive solid tumor (excluding CNS primary) with measurable disease
Cohort 2	*RET*-mutant MTC with measurable disease
Cohort 3	*RET*-fusion-positive primary CNS tumor with measurable disease
Cohort 4	Any patient with *RET* mutation/alteration not fitting Cohort 1 to 3 criteria, for example (but not limited to) • *RET*-mutant MTC with nonmeasurable disease • *RET*-fusion-positive solid tumor with nonmeasurable disease, or • *RET*-fusion-positive solid tumor with measurable disease and *RET* fusion identified by plasma cfDNA

Abbreviations: cfDNA = circulating free DNA; CNS = central nervous system; MTC = medullary thyroid cancer; RET = REarranged during Transfection.

The inclusion criteria allowed for the inclusion of patients aged 2 to 21 years (in eleven countries), as agreed in the PIP. This is also consistent with the claimed indication.

Treatments

Selpercatinib was administered orally twice daily (BID), with the dose based on body surface area.

Table 21. Study Intervention Administered

<table>
<tr><th>Parameter</th><th>Treatment Administered</th></tr>
<tr><td>Intervention name</td><td>Selpercatinib (LY3527723)</td></tr>
<tr><td>Type</td><td>Investigational drug</td></tr>
<tr><td>Dose formulation</td><td>Liquid suspension or simple blend capsules/tablets containing drug substance with a simple blend of excipients</td></tr>
<tr><td>Dosage level</td><td>Phase 1: Dose-finding and dose-escalation phases
<table>
<tr><th>Dose Level</th><th>Dose</th><th>Estimated Equivalent Adult Dose</th></tr>
<tr><td>-2</td><td>46 mg/m^2 BID</td><td>80 mg BID</td></tr>
<tr><td>-1</td><td>70 mg/m^2 BID</td><td>120 mg BID</td></tr>
<tr><td>1[a]</td><td>92 mg/m^2 BID</td><td>160 mg BID</td></tr>
<tr><td>2[a]</td><td>116 mg/m^2 BID</td><td>200 mg BID</td></tr>
<tr><td>3[a,b]</td><td>140 mg/m^2 BID</td><td>240 mg BID</td></tr>
</table>
Phase 2: Patients in Phase 2 received selpercatinib at the MTD or RP2D
Maximum dose in Phase 2 is 160 mg BID</td></tr>
<tr><td>Route of administration</td><td>Orally or via nasogastric or gastrostomy feeding tube.</td></tr>
<tr><td>Sourcing</td><td>Provided by Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company (Sponsor)</td></tr>
</table>

Abbreviations: BID = twice daily; MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose; SRC = Safety Review Committee. a The dose levels listed, that is, Dose Levels 1, 2, and 3 correspond to the Phase 1 dose Cohorts 1, 2, and 3, respectively. b Additional dose escalation may be considered based on the cumulative data (PK, safety, and efficacy); the actual dose determined by the SRC, not to exceed approximately 50% of the prior dose and considering capsule doses and capsule burden.

During Phase 1, only Dose Level 1 (92 mg/m²) was evaluated. As 92 mg/m² became the RP2D, all Phase 1 and Phase 2 patients were analysed together for PK, safety, and efficacy.

The starting dose level of 92 mg/m² BID (maximum 160 mg BID) was intended to deliver exposure equivalent to that of the recommended Phase 2 dose (RP2D) in adults.

Additionally, the dose and regimen are consistent with the current SmPC in adolescents.

Objectives /Outcomes/Endpoints

The primary objective of the Phase 1 portion of LIBRETTO-121 was to determine the safety profile, including dose-limiting toxicities, of selpercatinib.

The primary objective of the Phase 2 portion was to determine the objective response rate based on Response Evaluation Criteria in Solid Tumours (Version 1.1) or Response Assessment in Neuro-Oncology as appropriate to tumour type as determined by an independent review committee.

Table 22. Objectives and endpoints for Phase 1 and Phase 2 part of Loxo-121 study

Objectives	Endpoints
Phase 1	
Primary • To determine the safety, including DLTs, of the oral RET inhibitor selpercatinib in pediatric patients with an advanced solid or primary CNS tumor harboring an activating RET alteration	• Frequency, severity, and relatedness of TEAEs and SAEs, including DLTs in pediatric patients receiving selpercatinib
Secondary • To characterize the PK properties of selpercatinib in pediatric patients with advanced solid, or primary CNS tumors harboring an activating RET alteration • To identify the MTD and/or the appropriate dose of selpercatinib for further clinical investigation in this patient population • To describe the antitumor activity of selpercatinib in pediatric patients with advanced solid or primary CNS tumors harboring an activating RET alteration	• Plasma concentrations of selpercatinib and PK parameters, including, but not limited to AUC(0-24), C_{max}, t_{max}, degree of accumulation, and other characterizations • The MTD and/or the RP2D of selpercatinib in the pediatric patients • ORR and CBR based on RECIST 1.1 or RANO as appropriate to tumor type as determined by an IRC and treating investigator
Phase 2	
Primary • To determine the ORR as determined by an IRC and measured by the proportion of patients with best overall confirmed response of CR or PR by RECIST 1.1, or RANO criteria, as appropriate, following treatment with selpercatinib in pediatric patients with an advanced cancer harboring an activating RET alteration	• ORR based on RECIST 1.1 or RANO as appropriate to tumor type as determined by an IRC
Secondary • To determine the following in patients with advanced cancer harboring an activating RET alteration: o ORR based on the treating investigator's response assessment using RECIST 1.1 or RANO criteria, as appropriate to tumor type o DOR in patients with BOR of CR or PR as determined by 1) an IRC and 2) the treating investigator	• ORR based on RECIST 1.1 or RANO as appropriate to tumor type per the treating investigator's response assessment • DOR (IRC and treating investigator) • PFS (IRC and treating investigator) • OS • CBR (IRC and treating investigator) • Frequency, severity, and relatedness of TEAEs and SAEs, changes in hematology and blood chemistry values, and assessments of physical examinations, vital signs, and ECGs

○ PFS following initiation of selpercatinib by 1) an IRC and 2) the treating investigator ○ OS following initiation of selpercatinib ○ To evaluate the CBR based on the proportion of patients with BOR of CR, PR, or SD lasting 16 or more weeks following initiation of selpercatinib as determined by 1) an IRC and 2) the treating investigator • To assess the safety profile and tolerability of selpercatinib • To characterize the PK properties of selpercatinib in pediatric patients • To evaluate the concordance of prior molecular profiling that detected an activating RET alteration within the patient's tumor with diagnostic test(s) being evaluated by the Sponsor • To evaluate change from baseline in patient-reported pain at BOR visit as assessed by the Wong-Baker Faces Scale. • To assess the acceptability and palatability of selpercatinib tablets, including dispersed tablets, in patients under age 18.	• Plasma concentrations of selpercatinib and PK parameters, including, but not limited to AUC(0-24), C_{max}, t_{max}, degree of accumulation, and other characterizations. • The percent-positive agreement between prior molecular profiling that detected an RET alteration within the patient's tumor and diagnostic test(s) being evaluated by the Sponsor • Change from baseline in patient-reported pain at BOR visit as assessed by the Wong-Baker Faces Scale. • Assessment of tablet or dispersed tablet presentation, including acceptability and palatability by patient and/or caregiver
Tertiary/Exploratory • To determine the relationship between PK and drug effects, including efficacy and safety • To evaluate the serum tumor markers CEA and calcitonin before, during, and at the end of treatment with selpercatinib (for patients with MTC only) • To explore the association of clinical response categories with patient-reported pain, as assessed by the Wong-Baker Faces Scale • To explore the association of clinical response with HRQoL as assessed by the PedsQL-Core • To describe changes from baseline in patient-reported pain and HRQoL measures, as assessed by the Wong-Baker Faces Scale and the PedsQL-Core • To characterize *RET* gene fusions and mutations by molecular assays including NGS from tumor biopsies and circulating tumor DNA • To characterize concurrently activated oncogenic pathways in pre-treatment tumor biopsies with the aim of elucidating RET biology, and modifiers of response to selpercatinib • To assess changes in tumor molecular status in tumor biopsies and circulating tumor DNA obtained during treatment and after progression	• Characterize PK as it relates to study drug effects, including efficacy and safety • Changes in CEA and calcitonin (for patients with MTC only) • The association of clinical response with patient-reported pain, as assessed by the Wong-Baker Faces Scale • The association of clinical response with HRQoL as assessed by the PedsQL-Core • Changes from baseline in patient-reported pain and HRQoL measures, as assessed by the Wong-Baker Faces Scale and the PedsQL-Core • Type of *RET* gene fusions and mutations by molecular assays including NGS from tumor biopsies and circulating tumor DNA • Changes in tumor molecular status in tumor biopsies and circulating tumor DNA obtained during treatment and after progression on selpercatinib

on selpercatinib, with the aim of elucidating RET biology, modifiers of response, and mechanisms of acquired resistance to selpercatinib	

Abbreviations: AUC(0-24) = area under the concentration versus time curve from time 0 to 24 hours; BOR = best overall response; CBR = clinical benefit rate; C_{max} = maximum drug concentration; CNS = central nervous system; CR = complete response; DLT = dose-limiting toxicity; DOR = duration of response; ECG = electrocardiogram; HRQoL = health-related quality of life; IRC = independent review committee; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PedsQL-Core = Pediatrics Quality of Life - Core Module; PK = pharmacokinetic; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors; RET = Rearranged during Transfection; RP2D = recommended Phase 2 dose; SAE = serious adverse event; SD = stable disease; TEAE = treatment-emergent adverse event; t_{max} = time to maximum plasma concentration.

Sample size

Phase 1

A minimum of 3 patients had to be enrolled into a dose escalation cohort in order to define the MTD or RP2D of selpercatinib. The actual number of patients enrolled was dependent on the number of patients enrolled in each dose escalation cohort, the number of cohorts enrolled, and when DLTs occur before declaring an MTD or RP2D. The safety of the patients enrolled was ensured with careful monitoring and rules for escalation so that an excessive number of patients are not unnecessarily exposed to a dose level that exceeds the MTD.

If a dose level was evaluated for MTD/RP2D and the sponsor declared that dose level as the RP2D, and the enrolled patient population did not contain at least 2 patients aged 6 months to ≤2 years, then the Phase 2 expansion could continue for patients greater than 2 years of age. Up to 2 patients aged 6 months to ≤2 years will be overenrolled in the dose level and evaluated to ensure this age group also meets the MTD/RP2D safety determination. Once this milestone had been achieved, patients aged 6 months to ≤2 years may have been eligible to enroll in Phase 2. At least 5 patients aged 6 months to ≤2 years were to be enrolled across the Phase 2 cohorts.

Phase 2

Approximately 10 to 20 patients could be enrolled in each of the designated Phase 2 cohorts: at least 5 patients aged ≥2 and <12 years, and at least 5 patients aged ≥12 and <18 years were to be enrolled. Additional patients could be enrolled to better characterise the safety and efficacy of the selpercatinib RP2D.

The number of patients was determined largely by feasibility considerations owing to the extreme rarity of paediatric patients with an advanced cancer harbouring an activating RET alteration. Although the planned sample size was limited, it was anticipated that the objective response rate was high (≥50%) for each cohort evaluated. Any summary of objective response rate (ORR) for a group of at least 20 patients was estimated to provide approximately 75% power to achieve a lower boundary of a 2-sided 95% exact binomial confidence interval (CI) about the estimated ORR that exceeds 20%. Ruling out a lower limit of 20% is considered clinically meaningful in patients who have limited treatment options for their advanced disease.

Randomisation

Not applicable, this is a single-arm study.

Blinding (masking)

Not applicable, this is an open-label study.

Statistical methods

All confidence intervals (CIs) were given at a 2-sided 95% level, unless otherwise stated. Statistical analysis was performed using SAS software (SAS, version 9.1.2 or higher).

Continuous variables were summarised using descriptive statistics (that is, the number of patients, mean, median, standard deviation, minimum, and maximum). Categorical variables were summarised by frequency and its corresponding percentage.

Summaries of safety, baseline characteristics, and efficacy were generally performed and reported overall and separately for patients with (i) RET-mutant MTC, (ii) RET fusion-positive papillary thyroid cancer (PTC), and (iii) other RET fusion-positive tumours.

Considering that Study JZJJ is primarily conducted in paediatric patients, additional data summaries and listings were subgrouped specifically by categories of age at study entry. Sets of summaries of patients by age were grouped according to these categories:

- ≥ 6 months and < 2 years
- ≥ 2 years and < 12 years
- ≥ 12 years and < 18 years, and
- ≥ 18 years.

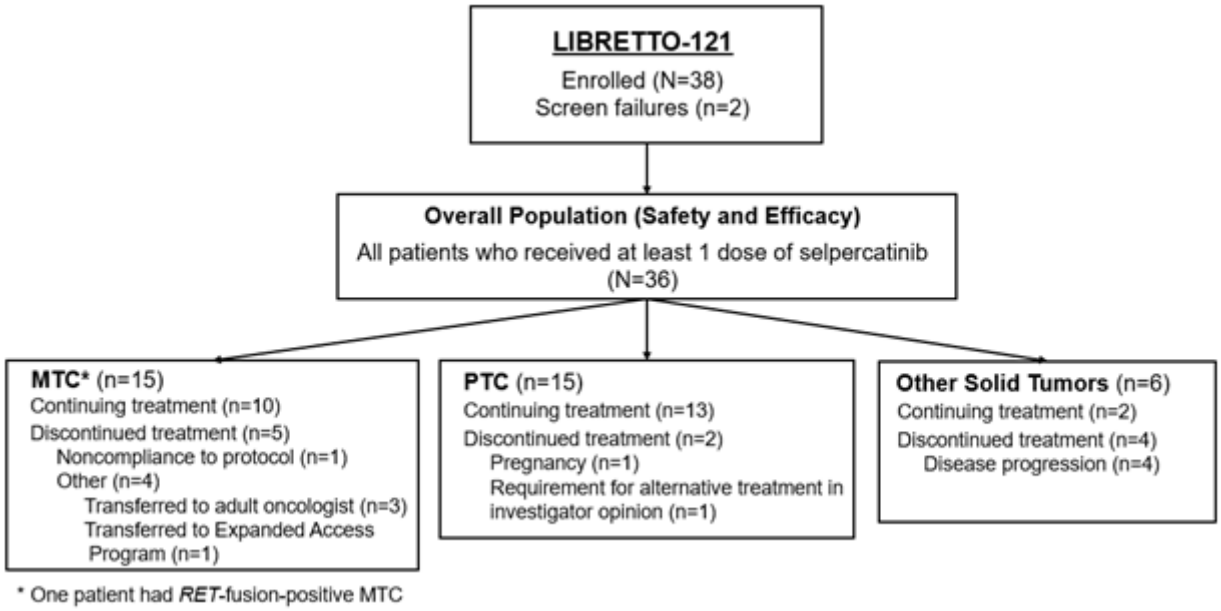
Data summaries or listings could be performed specific to certain geographical considerations (for example, summaries or listings of patients enrolled in east Asian countries).

Results

The MAH provided the final clinical study report with efficacy and safety results from LIBRETTO-121, with a data cutoff date of November 8, 2024, in paediatric patients with advanced solid or primary CNS tumours harbouring an activating *RET* alteration.

Participant flow

Figure 17. Study patient disposition flow diagram depicting LIBRETTO-121 analysis populations



Abbreviations: MTC = medullary thyroid cancer; n = number of subjects in the specified category; N = number of subjects in the analysis group; PTC = papillary thyroid cancer; *RET* = REarranged during Transfection.
Data cutoff date: 08 November 2024.

Table below provides the number of participants included in each analysis population.

Table 23. Analysis Populations for Study LIBRETTO-121

Population	Description	N
Enrolled	Patients who signed the informed consent/assent document	38
Safety and Efficacy[a]	All patients who received at least 1 dose of selpercatinib	36
MTC[b]	Includes patients with *RET*-altered MTC	15
RET-mutant MTC	Excluded MTC patients with *RET*-fusion-positive alterations	14
PTC	Includes patients with *RET*-fusion PTC	15
Other cancers	Includes patients with other solid tumor with *RET* alterations	6

Abbreviations: MTC = medullary thyroid cancer; N = number of patients in the analysis population; PTC = papillary thyroid cancer; RET = REarranged during Transfection.

[a] Safety and Efficacy Populations will be referred to as the **Overall Population** in this CSR.

[b] One patient who had *RET*-fusion-positive MTC.

Recruitment

The study was conducted at 27 centres that enrolled 36 patients in the United States of America, Japan, Australia, Italy, Canada, South Korea, France, Denmark, Germany, Spain, and the United Kingdom.

Study initiation date (first participant first visit): 13 June 2019

Data cutoff date for final analysis: 8 November 2024

LIBRETTO-121 is currently ongoing but closed to the recruitment of new patients.

Conduct of the study

Major protocol deviations for the TC Safety Population and Overall Safety Population are presented in the table below.

Table 24. Summary of Major Protocol Deviations Safety Analysis Set

	Total (N=36) n (%)	MTC (N=15) n (%)	PTC (N=15) n (%)	Other (N=6) n (%)
Patients with at least one CSR reportable protocol deviation	19 (52.8)	12 (80.0)	6 (40.0)	1 (16.7)
INVESTIGATIONAL PRODUCT	12 (33.3)	10 (66.7)	1 (6.7)	1 (16.7)
INFORMED CONSENT	6 (16.7)	5 (33.3)	1 (6.7)	0 (0.0)
RESTRICTED CONCOMITANT MEDICATION CHANGES	5 (13.9)	1 (6.7)	4 (26.7)	0 (0.0)
SAE REPORTING	3 (8.3)	2 (13.3)	0 (0.0)	1 (16.7)
EXCLUSION CRITERIA	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
STUDY PROCEDURES	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Patients with at least one CSR reportable protocol deviation related to COVID-19	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: CSR = Clinical Study Report; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; n = number of subjects in the specified category; PTC = Papillary Thyroid Cancer; SAE = Serious Adverse Event.

Baseline data

Demographics

The following table presents the patients demographics by Tumour Type Safety Analysis population.

Table 25. Summary of Demographics and Baseline Characteristics by Tumour Type Safety Analysis Set

	Total (N=36)	MTC (N=15)	PTC (N=15)	Other (N=6)
Age at Informed Consent/Assent (years)				
n	36	15	15	6
Mean	12.5	12.8	13.2	10.0
Standard Deviation	4.75	5.31	4.09	4.82
Median	13.0	13.0	12.0	9.5
Minimum	2	2	6	5
Maximum	20	20	20	15
Age Group (n, %)				
2 years to <6 years	3 (8.3)	2 (13.3)	0 (0.0)	1 (16.7)
6 years to <12 years	8 (22.2)	3 (20.0)	3 (20.0)	2 (33.3)
12 years to <18 years	20 (55.6)	7 (46.7)	10 (66.7)	3 (50.0)
18 years to <= 21 years	5 (13.9)	3 (20.0)	2 (13.3)	0 (0.0)
Sex (n, %)				
Male	19 (52.8)	9 (60.0)	8 (53.3)	2 (33.3)
Female	17 (47.2)	6 (40.0)	7 (46.7)	4 (66.7)
Race (n, %)				
White	17 (47.2)	11 (73.3)	6 (40.0)	0 (0.0)
Black or African American	3 (8.3)	2 (13.3)	0 (0.0)	1 (16.7)
Asian	10 (27.8)	0 (0.0)	7 (46.7)	3 (50.0)
Other	4 (11.1)	1 (6.7)	2 (13.3)	1 (16.7)
Missing	2 (5.6)	1 (6.7)	0 (0.0)	1 (16.7)
Ethnicity (n, %)				
Hispanic or Latino	7 (19.4)	2 (13.3)	4 (26.7)	1 (16.7)
Not Hispanic or Latino	26 (72.2)	11 (73.3)	11 (73.3)	4 (66.7)
Unknown	2 (5.6)	1 (6.7)	0 (0.0)	1 (16.7)
Missing	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)

Height (cm)				
n	36	15	15	6
Mean	150.2	154.1	152.9	134.0
Standard Deviation	25.58	32.29	17.10	21.43
Median	156.1	168.8	156.2	130.0
Minimum	75	75	117	115
Maximum	191	191	176	165
Height Z-Score*a				
n	33	14	13	6
Mean	-0.3	0.1	-0.3	-1.0
Standard Deviation	1.66	2.23	0.94	1.23
Median	-0.5	0.4	-0.6	-1.0
Minimum	-5	-5	-2	-3
Maximum	4	4	2	1
Weight (kg)				
n	36	15	15	6
Mean	44.4	44.6	48.2	34.5
Standard Deviation	20.80	21.59	19.67	21.84
Median	47.2	51.1	48.3	23.9
Minimum	10	10	19	17
Maximum	98	93	98	69
Weight Z-Score*a				
n	33	14	13	6
Mean	-0.7	-0.8	-0.2	-1.4
Standard Deviation	1.94	1.50	1.60	3.26
Median	-0.2	-0.3	0.1	-0.4
Minimum	-8	-4	-4	-8
Maximum	2	2	2	1
Body Surface Area (m^2)*b				
n	36	15	15	6
Mean	1.3	1.4	1.4	1.1
Standard Deviation	0.42	0.47	0.36	0.43
Median	1.4	1.5	1.5	0.9
Minimum	0	0	1	1
Maximum	2	2	2	2
Karnofsky/ Lansky Performance Status*c				
n	36	15	15	6
Mean	90.0	88.7	94.0	83.3
Standard Deviation	15.12	15.06	12.98	19.66
Median	100.0	100.0	100.0	90.0
Minimum	50	60	60	50
Maximum	100	100	100	100

Data Exported 10-Jan-2025, Visit Cutoff 08-Nov-2024
Abbreviations: CDC = Centers for Disease Control; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; n = number of
subjects in the specified category; PTC = Papillary Thyroid Cancer.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Baseline is defined as the last observation before the administration of selpercatinib.
*a Z-Score is calculated based on CDC growth charts. Z-Score is not available if the patient is greater than 20 years old.
*b Body surface area (BSA) is determined by the Mosteller (√((height (cm) × weight (kg))/3600)) formula.
*c Karnofsky Performance Status Score is applied for the subjects who are greater than or equal to 16 years. Lansky Performance is applied for the subjects who are less than 16 years.

Baseline Disease characteristics

Details of the pathologies presented are described in the following table:

Table 26. Baseline Disease Characteristics by Tumour Type Safety Analysis Set

Characteristics	Total (N=36)	MTC (N=15)	PTC (N=15)	Other (N=6)
Primary Diagnosis (n, %)				
Thyroid Cancer	30 (83.3)	15 (100.0)	15 (100.0)	0 (0.0)
Medullary Thyroid Cancer MTC	15 (41.7)	15 (100.0)	0 (0.0)	0 (0.0)
Papillary Thyroid Cancer	15 (41.7)	0 (0.0)	15 (100.0)	0 (0.0)
Sarcoma	5 (13.9)	0 (0.0)	0 (0.0)	5 (83.3)
Congenital (Infantile) Fibrosarcoma	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Malignant Peripheral Nerve Sheath Tumor	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Osteosarcoma	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Rhabdomyosarcoma	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Spindle Cell Sarcoma	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Other	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Stage at Study Entry (n, %)				
IB	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
II	8 (22.2)	0 (0.0)	8 (53.3)	0 (0.0)
III	2 (5.6)	2 (13.3)	0 (0.0)	0 (0.0)
IIIB	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
IV	14 (38.9)	5 (33.3)	5 (33.3)	4 (66.7)
IVB	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
IVC	6 (16.7)	6 (40.0)	0 (0.0)	0 (0.0)
Missing	3 (8.3)	1 (6.7)	1 (6.7)	1 (16.7)
Months since Initial Diagnosis				
n	36	15	15	6
Mean	28.16	25.52	29.26	31.98
Standard Deviation	28.891	35.448	22.011	30.426
Median	17.35	8.50	21.50	27.20
Minimum	0.1	0.1	1.0	2.5
Maximum	114.5	114.5	68.9	74.7
Metastatic Disease or Locally Advanced Disease (n, %)				
Metastatic	27 (75.0)	11 (73.3)	13 (86.7)	3 (50.0)
Locally Advanced	9 (25.0)	4 (26.7)	2 (13.3)	3 (50.0)

Months since Diagnosis of Metastatic Disease				
n	27	11	13	3
Mean	19.24	14.38	24.03	16.33
Standard Deviation	23.235	23.630	24.141	20.929
Median	8.70	6.40	13.50	4.30
Minimum	0.1	0.1	1.0	4.2
Maximum	71.4	71.4	68.9	40.5
CNS Metastases Status at Baseline by Investigator (n, %)				
Yes	2 (5.6)	1 (6.7)	0 (0.0)	1 (16.7)
No	34 (94.4)	14 (93.3)	15 (100.0)	5 (83.3)
Grade (n, %)				
Well Differentiated	6 (16.7)	0 (0.0)	6 (40.0)	0 (0.0)
Poorly Differentiated	6 (16.7)	3 (20.0)	1 (6.7)	2 (33.3)
Not Applicable	7 (19.4)	3 (20.0)	2 (13.3)	2 (33.3)
Unknown	16 (44.4)	8 (53.3)	6 (40.0)	2 (33.3)
Missing	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Presence of Cushing Disease Related to Primary Cancer (n, %)				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	36 (100.0)	15 (100.0)	15 (100.0)	6 (100.0)
Presence of Diarrhea for MTC patients at Baseline (n, %)				
Yes	5 (13.9)	5 (33.3)	0 (0.0)	0 (0.0)
No	10 (27.8)	10 (66.7)	0 (0.0)	0 (0.0)

Data Exported 10-Jan-2025, Visit Cutoff 08-Nov-2024
Abbreviations: CNS = Central Nervous System; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; n = number of subjects in the specified category; PTC = Papillary Thyroid Cancer.

RET alteration status

Table 27. Baseline Disease Characteristics – *RET* Alteration Status by Tumour type Safety Analysis Set

Characteristics	Total (N=36) n (%)	MTC (N=15) n (%)	PTC (N=15) n (%)	Other (N=6) n (%)
Documented RET Alteration				
Yes	36 (100.0)	15 (100.0)	15 (100.0)	6 (100.0)
RET Alteration Type				
Fusion	19 (52.8)	1 (6.7)	15 (100.0)	3 (50.0)
AKAP13-RET	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
CCDC6-RET	5 (13.9)	1 (6.7)	3 (20.0)	1 (16.7)
ERC1-RET	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
MYH10-RET	2 (5.6)	0 (0.0)	0 (0.0)	2 (33.3)
NCOA4-RET	7 (19.4)	0 (0.0)	7 (46.7)	0 (0.0)
TRIM24-RET	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
Unknown	2 (5.6)	0 (0.0)	2 (13.3)	0 (0.0)
Mutation	15 (41.7)	14 (93.3)	0 (0.0)	1 (16.7)
C634F/G/R/S/W/Y	4 (11.1)	3 (20.0)	0 (0.0)	1 (16.7)
L790F	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
M918T	10 (27.8)	10 (66.7)	0 (0.0)	0 (0.0)
Mutation at Exon 14 - S853L	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
V706M	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
RET Alteration, Type of Assay				
FISH	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
NGS	32 (88.9)	12 (80.0)	14 (93.3)	6 (100.0)
PCR	2 (5.6)	2 (13.3)	0 (0.0)	0 (0.0)
RT-PCR	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)

Data Exported 10-Jan-2025, Visit Cutoff 08-Nov-2024
Abbreviations: FISH = fluorescence in situ hybridization; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; NGS = next-generation sequencing; n = number of subjects in the specified category; PCR = polymerase chain reaction; PTC = Papillary Thyroid Cancer; RET = Rearranged During Transfection; RT-PCR = reverse transcription-polymerase chain reaction.

Prior cancer treatment

Table 28. Prior Cancer Treatment by Tumour Type Safety Analysis Set Excluding MTC Patients with RET Fusion

Characteristics	Total (N=35)	MTC (N=14)	PTC (N=15)	Other (N=6)
Received Prior Systemic Therapy (n, %)				
Yes	12 (34.3)	3 (21.4)	3 (20.0)	6 (100.0)
No	23 (65.7)	11 (78.6)	12 (80.0)	0 (0.0)
Number of Prior Systemic Regimens (n, %)				
0	23 (65.7)	11 (78.6)	12 (80.0)	0 (0.0)
1-2	9 (25.7)	3 (21.4)	3 (20.0)	3 (50.0)
3 or more	3 (8.6)	0 (0.0)	0 (0.0)	3 (50.0)
Number of Prior Systemic Regimens				
n	35	14	15	6
Mean	1.09	0.29	0.27	5.00
Standard Deviation	2.501	0.611	0.594	4.290
Median	0.00	0.00	0.00	4.00
Minimum	0.0	0.0	0.0	1.0
Maximum	10.0	2.0	2.0	10.0
Setting*a (n, %)				
Adjuvant	3 (8.6)	0 (0.0)	2 (13.3)	1 (16.7)
Neoadjuvant	1 (2.9)	0 (0.0)	0 (0.0)	1 (16.7)
Palliative	2 (5.7)	1 (7.1)	0 (0.0)	1 (16.7)
Curative	8 (22.9)	2 (14.3)	1 (6.7)	5 (83.3)
Prior Radiotherapy (n, %)				
Yes	12 (34.3)	2 (14.3)	6 (40.0)	4 (66.7)
No	23 (65.7)	12 (85.7)	9 (60.0)	2 (33.3)
Prior Surgery (n, %)				
Yes	30 (85.7)	10 (71.4)	15 (100.0)	5 (83.3)
No	5 (14.3)	4 (28.6)	0 (0.0)	1 (16.7)
Indication of Prior Surgery*a (n, %)				
Curative Intent	29 (82.9)	10 (71.4)	14 (93.3)	5 (83.3)
Palliative Intent	3 (8.6)	1 (7.1)	2 (13.3)	0 (0.0)
Diagnostic	7 (20.0)	2 (14.3)	3 (20.0)	2 (33.3)
Other	3 (8.6)	2 (14.3)	1 (6.7)	0 (0.0)

Concomitant therapy

The most frequently used therapeutic classes of concomitant medications in the RET Alteration Safety Analysis Set included anilides (83.3%), thyroid hormones (72.2%) and vitamin D and analogues (50.0%).

Exposure

Table 29. Selpercatinib Dose Intensity *RET* Alteration Status by Tumour type Safety Analysis Set

Status	Total (N=36)	MTC (N=15)	PTC (N=15)	Other (N=6)
Time on Treatment (TOT) (months)*a				
n	36	15	15	6
Mean	29.44	40.26	28.99	3.53
Standard Deviation	19.231	15.984	15.893	3.065
Median	30.26	41.00	30.06	2.74
Minimum	0.4	7.6	5.5	0.4
Maximum	62.4	62.4	52.7	7.9
Actual Dose Intensity (ADI) ((mg/m^2)/day)*b				
n	36	15	15	6
Mean	166.36	167.21	173.01	147.61
Standard Deviation	29.411	28.888	23.509	40.179
Median	176.84	178.91	177.29	160.44
Minimum	83.4	83.4	110.4	89.3
Maximum	204.9	189.5	204.9	184.0
Relative Dose Intensity (RDI) (%)*c				
n	36	15	15	6
Mean	90.41	90.88	94.03	80.22
Standard Deviation	15.984	15.700	12.777	21.836
Median	96.11	97.23	96.35	87.20
Minimum	45.3	45.3	60.0	48.5
Maximum	111.4	103.0	111.4	100.0
Relative Dose Intensity (RDI) Categories (n, %)				
>=90%	27 (75.0)	12 (80.0)	12 (80.0)	3 (50.0)
75 to <90%	3 (8.3)	1 (6.7)	1 (6.7)	1 (16.7)
50 to <75%	4 (11.1)	1 (6.7)	2 (13.3)	1 (16.7)
<50%	2 (5.6)	1 (6.7)	0 (0.0)	1 (16.7)
Compliance (%)*d				
n	36	15	15	6
Mean	91.47	91.57	95.25	81.75
Standard Deviation	15.011	15.123	12.047	19.352
Median	96.55	97.23	98.26	87.20
Minimum	48.0	48.0	62.5	57.7
Maximum	111.4	103.6	111.4	100.0
Compliance Categories (n, %)				
>=90%	27 (75.0)	12 (80.0)	12 (80.0)	3 (50.0)
75 to <90%	4 (11.1)	1 (6.7)	2 (13.3)	1 (16.7)
50 to <75%	4 (11.1)	1 (6.7)	1 (6.7)	2 (33.3)
<50%	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: ADI = Actual Dose Intensity; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; n = number of subjects in the specified category; PTC = Papillary Thyroid Cancer; RDI = Relative Dose Intensity; TOT = Time on Treatment.

Numbers analysed

Table 30. Summary of disposition by Tumour Type Safety and Efficacy Analysis Sets

	Total (N=38)	MTC (N=15)	PTC (N=15)	Other (N=6)
Subjects Enrolled*a	38	15	15	6
Screen Failure	2			
Subjects Treated*b	36 (100.0)	15 (100.0)	15 (100.0)	6 (100.0)
Subjects on Treatment	25 (69.4)	10 (66.7)	13 (86.7)	2 (33.3)
Treatment Continued Post-Progression*c	5 (13.9)	2 (13.3)	0 (0.0)	3 (50.0)
Treatment Continued Post-Progression Status*c				
Discontinued	4 (11.1)	1 (6.7)	0 (0.0)	3 (50.0)
Continuing	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Treatment Continued Post-Progression Category*c				
<14 days	2 (5.6)	0 (0.0)	0 (0.0)	2 (33.3)
>=14 days to 3 months	2 (5.6)	1 (6.7)	0 (0.0)	1 (16.7)
>=12 months	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Subjects Discontinued from Study Treatment	11 (30.6)	5 (33.3)	2 (13.3)	4 (66.7)
Disease progression	4 (11.1)	0 (0.0)	0 (0.0)	4 (66.7)
Pregnancy	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
Requirement for alternative treatment in the opinion of the investigator	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
Significant noncompliance to protocol	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Other	4 (11.1)	4 (26.7)	0 (0.0)	0 (0.0)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; PTC = Papillary Thyroid Cancer; RECIST = Response Evaluation Criteria in Solid Tumours; TOS = Time on Study; TOT = Time on Treatment.
Percentage is calculated using the number of treated subjects within each cohort as the denominator.
Tumor type was not collected for screen failures.
*a Subjects enrolled include all subjects who have signed the informed consent / assent document.
*b Only subjects with the first dose date on or before Visit Cutoff are included.
*c Based on Investigator assessments using RECIST (version 1.1).
*d On Study Death, defined as deaths during treatment or within 28 days of treatment discontinuation.
*e Safety analysis set includes all enrolled patients who receive 1 or more doses of selpercatinib.
*f Time on Treatment (TOT) (months) = (last dose date - first dose date + 1)/30.4375 for subjects who discontinued selpercatinil of the data cutoff date; TOT (months) = (data cutoff date - first dose date + 1)/30.4375 for subjects continuing to receive selpercatinib as of the data cutoff date.
*g Time on Study (TOS) (months) = (study exit date - first dose date + 1)/30.4375 for subjects who exited the study on or befor data cutoff date; TOS (months) = (data cutoff date - first dose date + 1)/30.4375 for subjects who were still in the treatme phase as of the data cutoff date; TOS (months) = (last visit date - first dose date + 1)/30.4375 for subjects who were in th long-term follow-up as of the data cut-off date.

Outcomes and estimation

Phase 1 portion Dose-Limiting Toxicity

The primary objective of the Phase 1 portion of the study was to determine the safety profile, including DLTs, of selpercatinib. A total of 3 patients with age of 10, 13, and 20 years, respectively, were included in the Phase 1 MTD/RP2D determination. However, no patients had DLT in the study. While the sample size was small, no differences from the known safety profile of selpercatinib were identified in this population.

The Phase 1 supported the RP2D (92 mg/m^2 BID, maximum 160 mg BID) of selpercatinib for paediatric and young adult patients when administered on a BID schedule.

Phase 2 Response to Study Intervention

The efficacy analysis was performed based on the Safety Analysis Set (Overall Population).

Primary Endpoints

Objective rate response (ORR) based on RECIST 1.1. according to the Independent Review Committee (IRC) assessment is the primary endpoint. ORR was defined as the proportion of patients who achieved a best overall response (BOR) of complete response (CR) or partial response (PR) based on confirmed responses by a ≥16 weeks assessment.

A total of 19 patients responded to selpercatinib treatment by the IRC assessment with an ORR of 52.8% (95% CI: 35.5, 69.6) including 10 patients who achieved CR.

The confirmed ORR based on IRC assessment for patients in the

- PTC Population (n=15) was 53.3% (95% CI: 26.6, 78.7)
- MTC Population (n=15) was 60.0% (95% CI: 32.3, 83.7)
- RET-mutant MTC patients (n=14) was 57.1% (95% CI: 28.9, 82.3), and
- Other Solid Tumours Population (n=6) was 33.3% (95% CI: 4.3, 77.7).

A total of 18 patients had non-measurable disease at baseline per the IRC assessment, of whom 6 were not evaluable (NE).

Table 31. Best Overall Response, Objective Response Rate, and Clinical Benefit Rate based on IRC Assessment by Tumour Type Safety Analysis Set

Status	Total (N=36)	MTC (N=15)	PTC (N=15)	Other (N=6)
Best Overall Response (n, %)*a				
Complete Response (CR)	10 (27.8)	6 (40.0)	4 (26.7)	0 (0.0)
Complete Response, Unconfirmed (uCR)	2 (5.6)	0 (0.0)	2 (13.3)	0 (0.0)
uCR*b	2 (5.6)	0 (0.0)	2 (13.3)	0 (0.0)
Partial Response (PR)	9 (25.0)	3 (20.0)	4 (26.7)	2 (33.3)
Partial Response, Unconfirmed (uPR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
uPR*b	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stable Disease (SD)	7 (19.4)	3 (20.0)	4 (26.7)	0 (0.0)
SD*b	7 (19.4)	3 (20.0)	4 (26.7)	0 (0.0)
Progressive Disease (PD)	2 (5.6)	0 (0.0)	0 (0.0)	2 (33.3)
Not Evaluable (NE)	6 (16.7)	3 (20.0)	1 (6.7)	2 (33.3)

Data Exported 10-Jan-2025, Visit Cutoff 08-Nov-2024 Abbreviations: CR = Complete Response; IRC = Independent Review Committee; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; n = number of subjects in the specified category; NE = Not Evaluable; PD = Progressive Disease; PR = Partial Response; PTC = Papillary Thyroid Cancer; RECIST = Response Evaluation Criteria in Solid Tumours; SD = Stable Disease; uCR = Complete Response, Unconfirmed; uPR = Partial Response, Unconfirmed. Percentage is calculated based on the number of patients in the column heading as the denominator. SD includes Non-CR/Non-PD. *a Based on Independent Review Committee (IRC) assessments using RECIST (version 1.1). *b Indicates uCR, uPR, or SD lasting >= 16 weeks following initiation of selpercatinib until the criteria for disease progression was first met. *c Objective Response Rate (%) is defined as the proportion of patients with Best Overall Response of confirmed CR or PR. Response was confirmed by a repeat assessment no less than 28 days later. *d Objective Response Rate, Confirmed and Unconfirmed (%) is defined as the proportion of patients with Best Overall Response of confirmed CR or PR, or uCR or uPR. *e Clinical Benefit Rate (%) is defined as the proportion of patients with Best Overall Response of confirmed CR, PR, or stable disease lasting 16 or more weeks for patients with uCR*b, uPR*b, or SD*b. Stable disease was measured from the date of the first dose of selpercatinib until the criteria for disease progression was first met. *f Clinical Benefit Rate, Confirmed and Unconfirmed (%) is defined as the proportion of patients with Best Overall Response of confirmed CR or PR, uCR, uPR, or SD lasting 16 or more weeks (SD*b). *g 95% Confidence Interval was calculated using Clopper-Pearson method.

Secondary Endpoint

Overall Response Rate by Investigator Assessment-Key Secondary Endpoint.

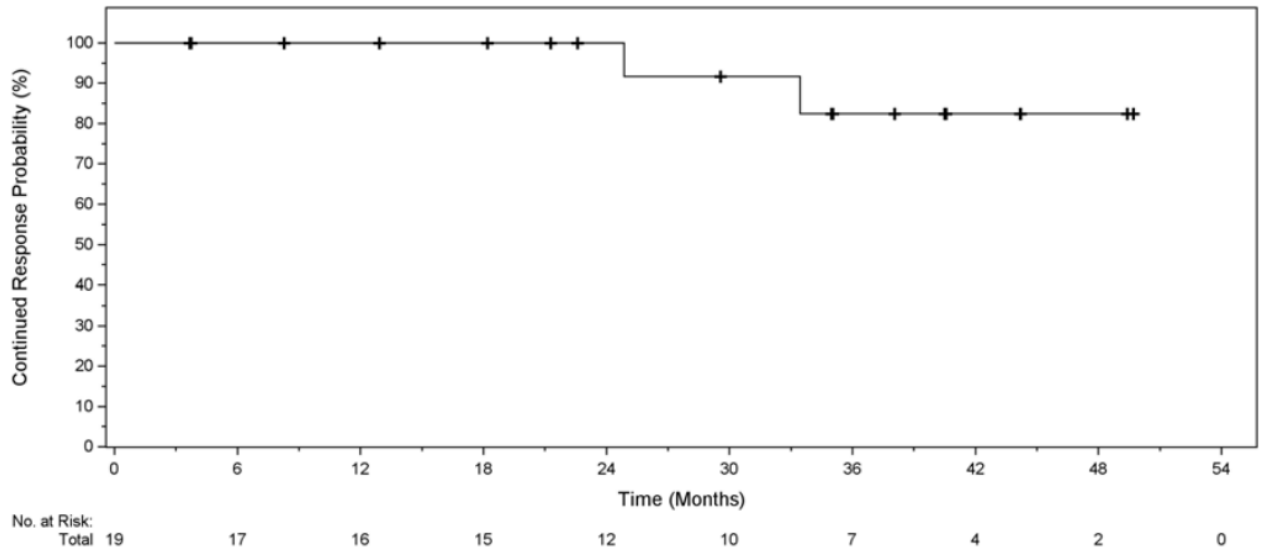
The ORR based on the investigator assessment is a key secondary endpoint. Confirmed ORR by the investigator assessment (36.1%) was lower in the Overall Population than the ORR by IRC assessment (52.8%). Confirmed ORR based on investigator assessment was also lower in the PTC and MTC Safety Populations than the IRC assessment.

Duration of Response

The median duration of response (DOR) by the IRC assessment was not reached (95% CI: 33.4, NE) neither overall nor across tumour types. The median follow-up time for DOR was

- 35.06 months (IQR: 18.2, 44.2) in the Overall Population,
- 39.59 months (IQR: 22.6, 49.4) in the MTC Population,
    - 44.19 months (IQR: 28.8, 49.4) in patients with RET-mutant MTC,
- 36.57 months (IQR: 25.4, 40.5) in the PTC Population, and
- 3.71 months (IQR: 3.7, 3.7) in the Other Solid Tumours Population.

Figure 18. Kaplan-Meier plot of duration of response based on IRC assessments Safety analysis set



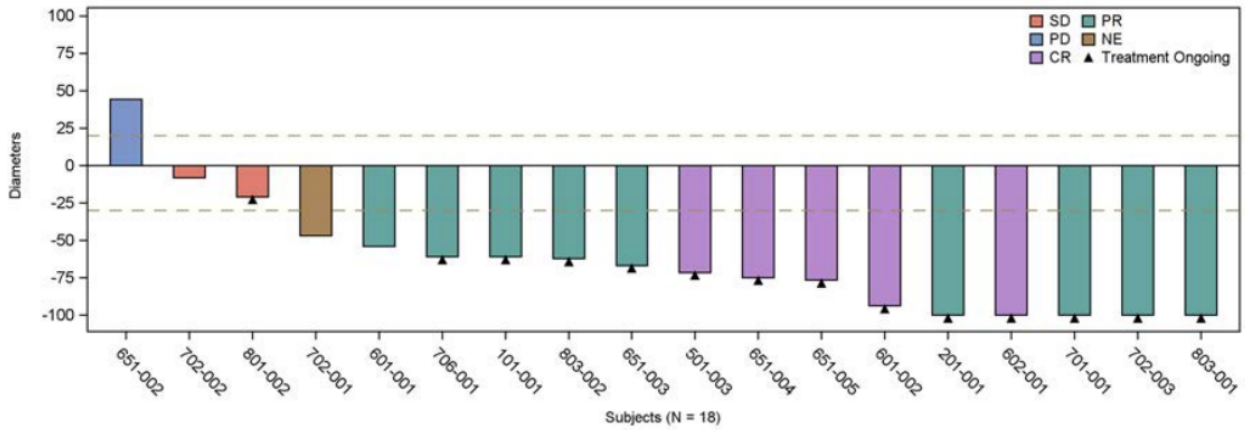
Abbreviations: IRC = Independent Review Committee; NE = Not Estimable; No. = Number.
Median duration of response (95% CI) is NE (33.4, NE) months.

Best change in tumour burden

Eighteen patients were eligible for change in tumour burden size analysis by the IRC. Best percentage change in tumour size was defined as the ratio of the best post baseline tumour size compared with the baseline assessment and is presented in figure below.

As determined by the IRC assessment, 17 (94.4%) patients demonstrated a reduction in tumour size from baseline.

Figure 19. Waterfall plot of best change in tumour burden based on IRC assessments Safety analysis set

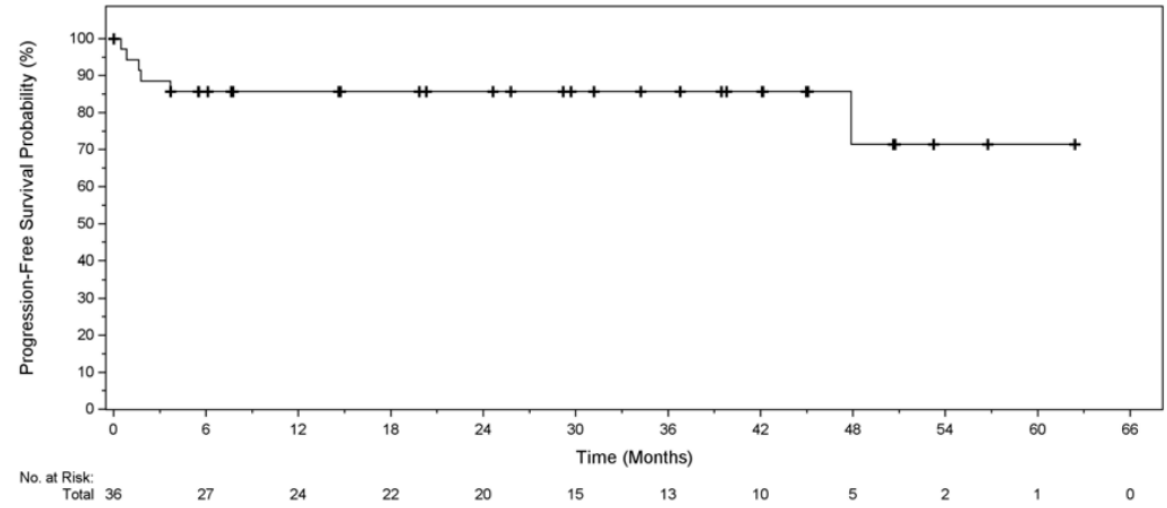


Abbreviations: CR = complete response; IRC = Independent Review Committee; N = number of subjects in the analysis group with a baseline and at least one postbaseline assessment; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.
For each subject, the best percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar. Baseline is defined as the last available measurement prior to the first dose of selpercatinib.

Progression-free survival

The median PFS data are not yet mature with a median follow-up time of 29.21 months and 5 PFS events reported in the Overall Population. PFS based on IRC and investigator assessments was generally consistent.

Figure 20. Kaplan-Meier plot of progression-free survival based on investigator assessments Safety analysis set

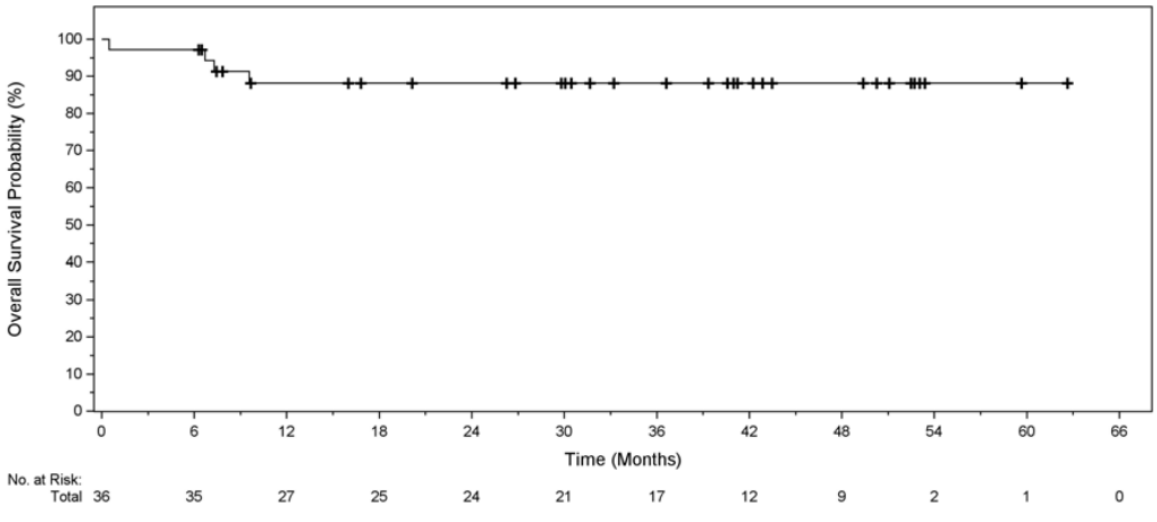


Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: NE = Not Estimable; No. = Number.
+ = censored.
Median progression-free survival (95% CI) is NE (47.9, NE) months.

Overall Survival

The median OS data are not yet considered mature, as only 4 events were reported at the data cutoff. The median follow-up time in the Overall Population was 39.36 months.

Figure 21. Kaplan-Meier plot of overall survival Safety analysis set



Abbreviation: No = number.

Main efficacy results

Table below summarizes the main efficacy results.

Table 32. Efficacy (ORR, DOR, PFS, and OS) Overall Population Data Cut-off Date: 08 November 2024

Analysis	Selpercatinib Overall Population N=36
ORR[a]	
n (%) 95% CI[b]	19 (52.8) (35.5, 69.6)
DOR[c]	
Responders, n	19
Median in months (95% CI)[d]	NE (33.4, NE)
Duration of follow-up[c]	
Median in months (IQR)	35.06 (18.2, 44.2)
DOR rates[c]	
Percentage (95% CI)[e]	100.0 (100.0, 100.0) at 12 months or more 100.0 (100.0, 100.0) at 24 months or more 82.5 (46.1, 95.3) at 36 months or more
PFS[c]	
Median in months (95% CI)[d]	NE (37.0, NE)
OS[c]	
Median in months (95% CI)[d]	NE (NE, NE)

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; IQR = interquartile range; n = number of patients in a specified category; N = number of patients in the analysis population; NE = not evaluable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response.

a ORR (%) is defined as the proportion of patients with best overall response of confirmed CR or PR. Response was confirmed by a repeat assessment no less than 28 days later.

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

c Estimate based on Kaplan-Meier method.

d 95% CI was calculated using the Brookmeyer and Crowley method.

e 95%CI was calculated using Greenwood's formula.

Patient-Reported Outcomes

Wong-Baker Faces Scale (WBFS)

In patients 3 years of age or older, pain was assessed by the WBFS. The 6-item ordinal scale ranges from 0 (no pain) to 10 (worst pain). Changes in WBFS pain score of 2 points or more from baseline were considered clinically meaningful change for both improvement and deterioration.

Baseline completion rates were 97.2% in the Overall Population. Median baseline PRO scores for the WBFS were 0 (0-10.0) in the Overall Population and 2.0 (2.0-10.0) in the WBFS ≥2 subgroup. Nearly all patients had stable or improved WBFS scores from baseline to BOR visit.

HRQoL by PedsQL-Core

The health-related quality of life (HRQoL) assessment was based on the Pediatrics Quality of Life - Core Module (PedsQL-Core) for the patient or their parent/caregiver. Changes in the PedsQL total score of 4.5 points or more from baseline were considered clinically meaningful change for both improvement and deterioration. The baseline completion rate for the Overall Population was 97.2%. Median baseline PRO score for PedsQL-Core was 69.6 (29.8-98.9) in the Overall Population

and 68.1 (29.8-85.9) in the WBFS ≥2 subgroup. Most patients had stable or improved PedsQL scores (total and individual domains) from baseline to BOR visit.

Ancillary analyses

Subgroup Analysis

The prespecified analysis subgroup for the population is by tumour type.

1- Analysis by tumour type

The below tables summarises the outcomes by tumour type based on IRC assessments.

- **RET-mutant MTC Population**

The results below were described in the population with a RET- mutant MTC (n=14) (excluding MTC Patients with *RET* Fusion (n=1)).

Table 33. Efficacy (ORR, DOR, PFS, and OS) MTC Population Data Cut-off Date: 08 November 2024

Analysis	Selpercatinib *RET*-mutant MTC Population N=14
ORR[a]	
n (%) 95% CI[b]	8 (57.1) (28.9, 82.3)
DOR[c]	
Responders, n	8
Median in months (95% CI)[d]	NE (24.9, NE)
Duration of follow-up[c]	
Median in months (IQR)	44.19 (28.8, 49.4)
DOR rates[c]	
Percentage (95% CI)[e]	100.0 (100.0, 100.0) at 12 months or more 100.0 (100.0, 100.0) at 24 months or more 66.7 (19.5, 90.4) at 36 months or more
PFS[c]	
Median in months (95% CI)[d]	NE (28.5, NE)
OS[c]	
Median in months (95% CI)[d]	NE (NE, NE)

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; IQR = interquartile range; MTC = medullary thyroid cancer; n = number of patients in a specified category; N = number of patients in the analysis population; NE = not evaluable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; *RET* = REarranged during Transfection.

a ORR (%) is defined as the proportion of patients with best overall response of confirmed CR or PR. Response was confirmed by a repeat assessment no less than 28 days later.

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

c Estimate based on Kaplan-Meier method.

d 95% CI was calculated using the Brookmeyer and Crowley method.

e 95% CI was calculated using Greenwood's formula.

The ORR was 57.1%, (8/14, 95%CI: 28.9, 82.3) as assessed by the IRC.

According to the IRC, at the data cut-off, 35.7% (5/14) of the responders had a CR, 21.4% (3/14) a PR.

Responses appeared durable, with median BICR-assessed DOR for responders not reached (95% CI: NE, NE) after a median follow-up of 44.19 months (interquartile range: 28.2, 49.4).

Both median PFS and OS in the RET mutant population were not reached, with a censoring rate of 86.7% and 100.0% and a median follow-up time of 31.24 and 41 months, respectively.

- **RET Fusion−Positive PTC Population**

The results below were described in the population with a RET-fusion PTC (n=15).

Table 34. Efficacy (ORR, DOR, PFS, and OS) PTC Population Data Cut-off Date: 08 November 2024

Analysis	Selpercatinib PTC Population N=15
ORR[a]	
n (%) 95% CI[b]	8 (53.3) (26.6, 78.7)
DOR[c]	
Responders, n	8
Median in months (95% CI)[d]	NE (NE, NE)
Duration of follow-up[c]	
Median in months (IQR)	36.57 (25.4, 40.5)
DOR rates[c]	
Percentage (95% CI)[e]	100.0 (100.0, 100.0) at 12 months or more 100.0 (100.0, 100.0) at 24 months or more 100.0 (100.0, 100.0) at 36 months or more
PFS[c]	
Median in months (95% CI)[d]	NE (NE, NE)
OS[c]	
Median in months (95% CI)[d]	NE (NE, NE)

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; IQR = interquartile range; n = number of patients in a specified category; N = number of patients in the analysis population; NE = not evaluable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PTC = papillary thyroid cancer.

a ORR (%) is defined as the proportion of patients with best overall response of confirmed CR or PR. Response was confirmed by a repeat assessment no less than 28 days later.

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

c Estimate based on Kaplan-Meier method.

d 95% CI was calculated using the Brookmeyer and Crowley method.

e 95% CI was calculated using Greenwood's formula.

The ORR was 53.3%, (8/15, 95%CI: 29.6, 78.7) as assessed by the IRC.

According to the IRC, at the data cut-off there was an equivalent complete or partial response rate (26.7% each, 4/15).

Responses appeared durable, with median BICR-assessed DOR for responders not reached (95% CI: NE, NE) after a median follow-up of 35,06 months (interquartile range: 18.2, 44.2).

Both median PFS and OS in the RET fusion dataset were not reached, with a censoring rate of 100% and 100% and a median follow-up time of 29.70 and 31.67 months, respectively.

- **Other Solid Tumours Population**

The results below were described in the population with others solid tumours (n=6).

Table 35. Efficacy (ORR, DOR, PFS, and OS) Others solid Tumours Population Data Cut-off Date: 08 November 2024

Analysis	Selpercatinib Other Solid Tumours Population N=6
ORR[a]	
n (%) (95% CI)[b]	2 (33.3) (4.3, 77.7)
DOR[c]	
Responders, n	2
Median in months (95% CI)[d]	NE (NE, NE)
Duration of follow-up[c]	
Median in months (IQR)	3.71 (3.7, 3.7)
DOR rates[c]	
Percentage (95% CI)[e]	NE (NE, NE) at 12 months or more NE (NE, NE) at 24 months or more NE (NE, NE) at 36 months or more
PFS[c]	
Median in months (95% CI)[d]	1.77 (0.5, NE)
OS[c]	
Median in months (95% CI)[d]	7.29 (0.5, NE)

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; IQR = interquartile range; n = number of patients in a specified category; N = number of patients in the analysis population; NE = not evaluable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response.

a ORR (%) is defined as the proportion of patients with best overall response of confirmed CR or PR. Response was confirmed by a repeat assessment no less than 28 days later.

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

c Estimate based on Kaplan-Meier method.

d 95% CI was calculated using the Brookmeyer and Crowley method.

e 95% CI was calculated using Greenwood's formula.

The ORR was 33.3%, (95%CI: 4.3, 77.7) as assessed by the IRC.

According to the IRC, at the data cut-off, 33.3% (2/6) patients responded to selpercatinib treatment, both with PR. Median BICR-assessed confirmed DOR for responders not reached (95% CI: NE, NE) after a median follow-up of 3.1 months (interquartile range: 3.7, 3.7).

Both median PFS and OS in the RET integrated dataset were not reached, with a censoring rate of 50% and 33.3% and a median follow-up time of 5.52 and 7.85 months, respectively.

2- Analysis by age group

The below table summarises the outcomes by age group based on IRC assessments.

Table 36. Efficacy (ORR, DOR, PFS, and OS) by Age Group and Tumour Type
Data Cut-off Date: 08 November 2024

	Overall Population[a] N = 36	MTC population[b] N=15	PTC Population N=15
Age Group, N			
Age 2 to <6 years	3	2	0
Age 6 to <12 years	8	3	3
Age 12 to <18 years	20	7	10
Age 18 to ≤ 21 years	5	3	2
ORR (by IRC)[c] n (%) (95% CI)[d]			
Age 2 to <6 years	2 (66.7) 9.4, 99.2	2 (100.0) 15.8, 100.0	-
Age 6 to <12 years	5 (62.5) 24.5, 91.5	3 (100.0) 29.2, 100.0	1 (33.3) 0.8, 90.6
Age 12 to <18 years	11 (55.0) 31.5, 76.9	4 (57.1) 18.4, 90.1	6 (60.0) 26.2, 87.8
Age 18 to ≤21 years	1 (20.0) 0.5, 71.6	0 (0.0) 0.0, 70.8	1 (50.0) 1.3, 98.7
DOR[e] Median in months (95% CI)[f]			
Age 2 to <6 years	NE (NE, NE)	NE (NE, NE)	-
Age 6 to <12 years	NE (33.4, NE)	NE (33.4, NE)	NE (NE, NE)
Age 12 to <18 years	NE (24.9, NE)	NE (24.9, NE)	NE (NE, NE)
Age 18 to ≤21 years	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Duration of follow-up[e] Median in months			
Age 2 to <6 years	28.99	28.99	-
Age 6 to <12 years	34.99	42.20	12.94
Age 12 to <18 years	35.06	33.40	36.57
Age 18 to ≤21 years	40.57	NE	40.57
PFS[e,g] Median in months (95% CI)[f]			
Age 2 to <6 years	NE (0.5, NE)	NE (NE, NE)	-
Age 6 to <12 years	36.99 (1.8, NE)	NE (37.0, NE)	NE (NE, NE)
Age 12 to <18 years	NE (28.5, NE)	NE (28.5, NE)	NE (NE, NE)
Age 18 to ≤21 years	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
OS[e,h] Median in months (95% CI)[f]			
	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; IRC = independent review committee; MTC = medullary thyroid cancer; n = number of patients in a specified category; N = number of patients in the analysis population; NE = not evaluable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PTC = papillary thyroid cancer; *RET* = REarranged during Transfection.

a Includes data from subjects with Other tumour types.

b The **MTC Population** by age group and tumour type efficacy analysis includes 1 patient with *RET* fusion−positive MTC; however, this patient was 13 years old at the time of enrolment and, therefore, does not impact the efficacy conclusions for the under 12 years age groups.

c ORR (%) is defined as the proportion of patients with best overall response of confirmed CR or PR. Response was confirmed by a repeat assessment no less than 28 days later.

d 95% CI was calculated using the Clopper-Pearson method.

e Estimate based on Kaplan-Meier method.

f 95% CI was calculated using the Brookmeyer and Crowley method.

g Except for the Overall Population age group 6 to <12 years, PFS was not estimable across tumour type and age groups.

h OS was not estimable across age groups (NE regardless of age group 2 to <6 years, 6 to <12 years, 12 to <18 years, and 18 to ≤21 years).

In vitro biomarker test for patient selection for efficacy

The presence of a *RET* gene alteration (mutation or fusion) was assessed by FISH, NGS, PCR or RT-PCR *in vitro* tests (see section 'Baseline disease characteristics').

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37. Summary of Efficacy for study LIBRETTO-121

Title: A Phase 1/2 Study of the Oral RET Inhibitor LOXO 292 in Paediatric Patients with Advanced RET-Altered Solid or Primary Central Nervous System Tumours			
Study identifier	LOXO-RET-18036 (J2G-OX-JZJJ); LIBRETTO-121		
Design	This is a multicenter, open-label, Phase 1/2 study in paediatric patients with advanced solid or primary CNS tumours harboring an activating RET alteration. This study includes 2 parts: Phase 1 (dose escalation) and Phase 2 (dose expansion)		
	Duration of main phase:		Study initiation date: 13 June 2019 (first patient first visit) End date: 08 November 2024 (data cutoff date for the final clinical study report).
Hypothesis	Exploratory: single-arm treatment. For each cohort evaluated, a true ORR of ≥ 50% is hypothesized when selpercatinib is administered to such patients.		
Treatments groups	Selpercatinib		Phase 2: 92mg/m² N=36
Endpoints and definitions	Primary endpoint	ORR based on RECIST 1.1 or RANO as appropriate to tumour type as determined by an IRC	ORR was defined as the proportion of patients who achieved a BOR of complete response or partial response. Response was confirmed by a repeat assessment no less than 28 days later.

	Secondary	ORR based on RECIST 1.1 or RANO as appropriate to tumour type per the treating investigator's response assessment	ORR was defined as the proportion of patients who achieved a BOR of complete response or partial response.
	Secondary	DOR based on IRC and Investigator assessment)	Time from the first documented response to the earliest date of documented disease progression or death (regardless of cause) for the patients with a confirmed CR or PR
	Secondary	PFS based on IRC and Investigator assessment	PFS is defined as the number of months elapsed between the date of the first dose of selpercatinib and the earliest date of documented disease progression or death (whatever the cause).
	Secondary	OS	OS is defined as the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause). Patients who are alive or lost to follow-up as of the data cutoff date will be right-censored. The censoring date will be determined from the date the patient was last known to be alive.
	Secondary	To assess the safety profile and tolerability of selpercatinib	Frequency, severity, and relatedness of TEAEs and SAEs, changes in hematology and blood chemistry values, and assessments of physical examinations, vital signs, and ECGs.
Database lock	12 December 2024		
Results and Analysis			
Analysis description	**Primary Analysis : Objective Response Rate by IRC**		
Analysis population and time point description	Paediatric and adolescent patients with advanced solid or primary CNS tumours harbouring an activating *RET* alteration. Data cutoff date: 08 November 2024.		

Descriptive statistics and estimate variability	Treatment group	Selpercatinib
	Number of subject	N=36
	Number of responder	N=19 (10CR, 9PR)
	Objective response rate (95% CI)	52.8% (35.5, 69.6)
	Duration of response - Median (95% CI)	NE (33.4, NE)
	Progression-free survival (months) - Median (95% CI)	NE (37.0, NE)
	Overall survival (months) - Median (95% CI)	NE (NE, NE)
	Duration of follow-up - Median (95% CI)	35.1 months (18.2, 44.2)
Notes	Patients with measurable or evaluable disease are included in the analysis	

2.4.2.2. Discussion on clinical efficacy

In the frame context of this application, the MAH is seeking for an extension of indication to paediatric patients **from 2 years to 11 years of age**. The claimed wording of indication is the following:

*Retsevmo as monotherapy is indicated for the treatment of adults and **paediatric patients 2 years** and older with:*

- *advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)*
- *advanced RET-mutant medullary thyroid cancer (MTC), and*
- *advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted.*

To note, NSCLC does not occur in paediatric patients, so an extension to paediatric patients for this population is not being sought by the MAH.

Design and conduct of clinical studies

LIBRETTO-121 (JZJJ) is a Phase I/II open-label, dose escalation and expansion study for selpercatinib in paediatric patients with advanced solid or primary CNS tumours harbouring an activating *RET* alteration.

The Phase 1 supported the RP2D (92 mg/m² BID, maximum 160 mg BID) of selpercatinib for paediatric and young adult patients when administered on a BID schedule.

It is important to note that the open-label single-arm design remains exploratory.

Overall, inclusion and exclusion criteria are considered acceptable. Selection criteria allowed to include patients between 6 months and 21 years old of age, with actual enrolment of patients 2 to 20 years of age. This was in line with the agreed PIP.

Overall, a total of 36 patients were enrolled in LIBRETTO-121 study. The dose escalation phase 1 aimed at MTD/DLT assessment in children. Paediatric patients treated at 92 mg/m^2 (up to 160 mg BID) had a similar exposure as adults treated with 160 mg BID at steady state on cycle 1 day 8, using the capsule formulation.

The evaluation of selpercatinib efficacy based on confirmed ORR by BRIC was the primary objective of the dose expansion phase (phase 2). The primary endpoint is considered an acceptable endpoint in the context of non-controlled single arm data to evaluate drug activity. The secondary endpoints which are ORR based on Investigator assessment using RECIST v1.1, duration of response (DoR), progression-free survival (PFS) based on IRC and Investigator assessment, and overall survival (OS), are relevant. However, interpretation of time-based endpoints of progression-free survival (PFS) and overall survival (OS) is generally hampered by the single-arm design and further by the fact that the dataset includes different tumour types that may have different natural history/prognosis.

A minority of paediatric patients under age 12 years were included in this pivotal study (30.5%, 11/36). The presence of alterations in the *RET* gene was assessed by various nucleic acid assays.

Efficacy data and additional analyses

Overall, 38 paediatric patients with *RET*-Altered solid tumours were screened and 36 were enrolled. All of them were included in the Efficacy Analysis Set. All paediatric patients included in the dataset had tumours that harbour an activating *RET* alteration with no evidence of co-occurrent mutations, not previously treated with *RET* inhibitors, with measurable or evaluable disease at baseline, who received at least 1 dose of selpercatinib. Patient had a median age at enrolment of 13 years, ranging from 2 to 20 years. Overall, only 8 patients between 2 and 12 years with thyroid cancer were included (3 with PTC and 5 with MTC). The sex ratio was around 1 and most patients were White and with good performance status.

Tumour types included *RET*-mutant medullary thyroid cancer (MTC, n = 15), *RET* fusion-positive papillary thyroid cancer (PTC, n = 15), or other *RET* alteration solid tumour (n = 6).

All (100%) had metastatic or locally advanced disease (75.0%, metastatic disease and 25.0%, locally advanced disease) at study entry, which is in line with claimed indication (i.e. locally advanced or metastatic cancer). More than 60% of patients had not received any prior systemic treatment (23/35; 65.7%). All patients with Other tumour type (n = 6, 100%) had already received systemic treatment whereas patients with thyroid tumour were mostly naive to systemic treatment (~80 %, 23/29).

The efficacy analysis supporting the extension of the age population for the MTC, PTC and Other tumour indications is based on a total of 36 paediatric patients with RET-Altered solid tumours.

Specifically, 11 (30.6%) patients were <12 years including 3 of them under 6 years which represents only 30% of the population targeted by the extension of indication (as adolescents ≥12 years were already included in the approved indications for PTC and MTC).

The median duration of survival follow-up was 39.36 months. More than half of the patients (25/36, 69.4%) are still taking selpercatinib, with PD being the most common reason for treatment discontinuation.

In the efficacy dataset (all included patients), the overall ORR was 52.8% (19/36), (95% CI: 35.5, 69.6), with a complete response (CR) rate (52.6%, 10/19) and 47.4% (9/19) of PR.

Responses appeared durable, with median BICR-assessed confirmed DOR for responders not reached (95% CI: 33.4, NE) after a median follow-up of 35.06 months (interquartile range: 18.2, 44.2).

Both median PFS and OS in the RET integrated dataset were not reached, with a censoring rate of 86.1% and 88.9% and a median follow-up time of 29.21 and 39.36 months, respectively. As commented above, PFS and OS are of difficult interpretation due to the size and type of dataset as well as the single arm design.

Almost all patients, regardless of age and tumour type, reported improvement or stability in their quality of life with improvement or stability in pain. However, the observed improvement is subject to important methodological limitations, as the physician, patients, and parents were aware of the treatment allocation.

Subgroup analyses

Analysis by tumour type

1- RET-mutant MTC

ORR was 57.1%, (8/14), (95% CI: 28.9, 82.3), with 62.5% (5/8) complete response (CR) rate and 37.5% (3/8) of PR. This level of response appears lower compared to the overall response rate shown by selpercatinib in the adult context (77.6% in pre-treated patients (EMEA/H/C/005375/R/0026) and 82.5% in naive patients (EMEA/H/C/005375/R/0026)).

In the population targeted by this extension of indication (2 to 11 years), an objective response was observed in all patients (n=5, 100%) with RET-mutant MTC, in this age group.

2- RET fusion−positive PTC

ORR was 53.3% (8/15), (95% CI: 26.6, 78.7), with an equivalent complete and partial response rate (50% each). This level of response appears lower compared to the overall response rate shown by selpercatinib in the adult context (85.4% in pre-treated patients (EMEA/H/C/005375/R/0026)) and 95.8% % in naive patients, (EMEA/H/C/005375/II/0021)).

In the population targeted by this extension of indication (2 to 11 years), an objective response was observed only in 1 of 3 (33%) patients with RET-fusion PTC, in this age group.

3- Other Solid Tumours

In the population targeted by this extension of indication (2 to 11 years), an objective response was observed only in 1 of 3 (33%) patients with RET alteration positive solid tumours, in this age group.

Analysis by age group

When analysed by age, responses were seen across all age subgroups analysed: <6 years ORR 66.7% (2/3); 6-<12 years ORR 62.5% (5/8); 12-<18 years ORR 55% (11/20) and 18-≤21 years ORR 20% (1/5). The overall ORR in the paediatric dataset does not appear to be determined by the youngest patients (37%, 7/19) but by those already included in approved indications of the marketing authorisation. In the population targeted by this extension of indication (2 to 11 years), an objective response was observed in 7 patients: 5 patients (100%) with RET-mutant MTC, 1 patient with RET-fusion PTC (33.3%) and 1 patient with RET-fusion positive solid tumours (33.3%).

Although limited, data show a consistent ORR across age groups and with that reported in a larger adult/adolescent dataset.

In conclusion, efficacy results in paediatric patients aged 2 to 11 years with thyroid cancer with RET alterations suggest observed tumour reduction could be attributed to selpercatinib.

Hereditary MTC is characterised by germline mutations in the *RET* proto-oncogene. The underlying genetic cause of the disease is identical in paediatric and adult patients, therefore the activity of selpercatinib in paediatric patients with this disease could be expected to be similar to that in adults. Although the number of patients was low, the response rate was considered promising, albeit lower than reported adult data.

Differences in paediatric and adult results were analysed, and issues that could explain the lower response were identified, i.e. more lines of pre-treatment in the paediatric study population, and inclusion of paediatric patients with non-measurable disease, for who response will be difficult to detect.

To support the extension of the indication of selpercatinib to the site and histology independent RET alteration positive solid tumours in paediatric patients, a data form 6 paediatric patients with mixed tumour types was presented, showing an overall confirmed ORR (33.3% (95% CI: 4.3, 77.7)) in 2 out of 6 patients and median DOR not reached, after a median follow-up of 3.1 months. The low number of responders (2) and the limited follow-up (3.1 months) makes it challenging to conclude on the clinical benefit of selpercatinib in this paediatric population. No direct comparison of the pathophysiology of these tumours in children and adults is possible. However constitutive RET activation is the common mechanism of disease, independent of age.

Additional considerations

In the context of the Conditional Marketing Authorisation (CMA) for Retsevmo, with the current application the following specific obligation (SOB) is considered fulfilled, and therefore it is recommended that it is deleted from the Annex II: *In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive thyroid cancer, the MAH should submit the final data from the study LIBRETTO-121 (Due date: 30 June 2025).*

2.4.2.3. Conclusions on the clinical efficacy

The clinical efficacy data provided is considered acceptable to support the extension of the indication to paediatric patients aged 2 years and older for the Retsevmo indications of MTC, PTC, and histology-independent tumours.

2.4.3. Clinical safety

Introduction

A safety analysis from the Overall Population in LIBRETTO-121 provides the primary basis for the safety profile of selpercatinib in paediatric patients with advanced solid tumours with RET alterations. As of the 08 November 2024 data cut-off, 36 patients have been enrolled and received at least 1 dose of selpercatinib at RP2D (92 mg/m^2 BID, maximum 160 mg BID).

Disposition and Characteristics of Patient Population

Disease characteristics

As of the data cutoff, 36 patients were enrolled in the Overall Population, which included

- 15 patients in the MTC Population,
- 15 patients in the PTC Population,
- and 6 patients in the Other Solid Tumours Population.

At the time of enrolment, all 36 patients had a history of locally advanced or metastatic disease and the most common tumour types were medullary thyroid cancer and papillary thyroid cancer.

For Overall Population, the median time since initial diagnosis and metastatic disease was 17.35 months and 8.7 months, respectively. Demographic and baseline characteristics in the safety population reflected the enrolment criteria and were representative of the general population of youth and adolescents with advanced RET-altered solid tumours.

Please refer to AR section Clinical Efficacy for more details regarding patient population.

Patient exposure

Selpercatinib Exposure

As of the 08 November 2024 data cut-off date, the paediatric safety database for LIBRETTO-121 included 36 study participants exposed to selpercatinib at any dose. All 36 patients comprising the Overall Population received at least 1 dose of selpercatinib. The mean duration of selpercatinib exposure was 29.44 months, ranging from 0.4 to 62.4 months.

The median relative dose intensity was 96.11%, which provides evidence of the favourable tolerability of selpercatinib.

The median duration of treatment in months was

- 30.26 months for the Overall Population
- 41.00 months for the MTC Population
- 30.06 months for the PTC Population, and
- 2.74 months for the Other Solid Tumours Population.

The median duration of treatment of the Other Solid Tumours Population is short due to rapid progression of disease, when experienced.

Table 38. Selpercatinib Drug Dosing, Intensities and Compliance by Tumour Type (Safety Analysis Set)

Status	Total (N=36)	MTC (N=15)	PTC (N=15)	Other (N=6)
Time on Treatment (TOT) (months)*a				
n	36	15	15	6
Mean	29.44	40.26	28.99	3.53
Standard Deviation	19.231	15.984	15.893	3.065
Median	30.26	41.00	30.06	2.74
Minimum	0.4	7.6	5.5	0.4
Maximum	62.4	62.4	52.7	7.9
Actual Dose Intensity (ADI) ((mg/m^2)/day)*b				
n	36	15	15	6
Mean	166.36	167.21	173.01	147.61
Standard Deviation	29.411	28.888	23.509	40.179
Median	176.84	178.91	177.29	160.44
Minimum	83.4	83.4	110.4	89.3
Maximum	204.9	189.5	204.9	184.0
Relative Dose Intensity (RDI) (%)*c				
n	36	15	15	6
Mean	90.41	90.88	94.03	80.22
Standard Deviation	15.984	15.700	12.777	21.836
Median	96.11	97.23	96.35	87.20
Minimum	45.3	45.3	60.0	48.5
Maximum	111.4	103.0	111.4	100.0
Relative Dose Intensity (RDI) Categories (n, %)				
>=90%	27 (75.0)	12 (80.0)	12 (80.0)	3 (50.0)
75 to <90%	3 (8.3)	1 (6.7)	1 (6.7)	1 (16.7)
50 to <75%	4 (11.1)	1 (6.7)	2 (13.3)	1 (16.7)
<50%	2 (5.6)	1 (6.7)	0 (0.0)	1 (16.7)
Compliance (%)*d				
n	36	15	15	6
Mean	91.47	91.57	95.25	81.75
Standard Deviation	15.011	15.123	12.047	19.352
Median	96.55	97.23	98.26	87.20
Minimum	48.0	48.0	62.5	57.7
Maximum	111.4	103.6	111.4	100.0
Compliance Categories (n, %)				
>=90%	27 (75.0)	12 (80.0)	12 (80.0)	3 (50.0)
75 to <90%	4 (11.1)	1 (6.7)	2 (13.3)	1 (16.7)
50 to <75%	4 (11.1)	1 (6.7)	1 (6.7)	2 (33.3)
<50%	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: ADI = Actual Dose Intensity; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; n = number of subjects in the specified category; PTC = Papillary Thyroid Cancer; RDI = Relative Dose Intensity; TOT = Time on Treatment.
Percentage is calculated using the number of subjects in the column heading as the denominator.
*a TOT (months) = (last dose date - first dose date + 1)/30.4375 for subjects who discontinued selpercatinib as of the data cutoff date; TOT (months) = (data cutoff date - first dose date + 1)/30.4375 for subjects continuing to receive selpercatinib as of the data cutoff date.
*b ADI ((mg/m^2)/day) = actual cumulative dose of selpercatinib (mg/m^2) received divided by TOT (days).
*c RDI (%) = (ADI/PDI)*100%. Planned Dose Intensity (PDI) ((mg/m^2)/day) = assigned dose level (mg/m^2)/day for dosing schedule; PDI = assigned dose level (mg/m^2)* 2/day for BID dosing schedule. The PDI will be calculated taking into account the starting dose and the escalated dose if applicable. The PDI is 92*2=184 (mg/m^2)/day.
*d Compliance is defined as the proportion of treatment that is actually taken, relative to what is planned, after accounting for dose adjustments due to adverse events.

Adverse events

Table 39. Overview of Adverse Events by Tumour Type (Safety Analysis Set)

	Total (N=36) n (%)	MTC (N=15) n (%)	PTC (N=15) n (%)	Other (N=6) n (%)
Patients with TEAEs	35 (97.2)	15 (100.0)	15 (100.0)	5 (83.3)
Patients with TEAEs Related to selpercatinib	33 (91.7)	15 (100.0)	15 (100.0)	3 (50.0)
Patients with TEAEs Maximum Severity Greater or Equal to 3	19 (52.8)	9 (60.0)	7 (46.7)	3 (50.0)
Patients with TEAEs Maximum Severity Greater or Equal to 3 and Related to selpercatinib	13 (36.1)	7 (46.7)	5 (33.3)	1 (16.7)
Patients with Serious TEAEs	15 (41.7)	8 (53.3)	4 (26.7)	3 (50.0)
Patients with Serious TEAEs and Related to selpercatinib	5 (13.9)	1 (6.7)	3 (20.0)	1 (16.7)

Patients with Fatal TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with Fatal TEAEs Related to selpercatinib	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with TEAEs and Action Taken of selpercatinib Permanently Discontinued	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
Patients with TEAEs and Action Taken of selpercatinib Permanently Discontinued and Related to selpercatinib	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DLT*a	0/4 (0.0)			
95% CI*b	(0.0, 60.2)			

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: AE = Adverse Event; CI = Confidence Interval; CTCAE = Common Terminology Criteria for Adverse Events; DLT = Dose-Limiting
Toxicity; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; n = number of subjects in the specified category; PTC = Papillary Thyroid Cancer; TEAE = Treatment-Emergent Adverse Event.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Treatment-emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of selpercatinib.
Severity grade assignment based on CTCAE (v5.0): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening/debilitating), Grade 5 (fatal).
*a The observed DLT rate = the number of patients who experienced DLT / DLT Analysis Set subjects * 100. Multiple concurrent AEs Leading to DLT are considered as a single event.
*b Two-sided 95% exact binomial CI is presented.

Table 40. Overview of Adverse Events by Age Group (Safety Analysis Set)

	Total (N=36) n (%)	2 to <6 years (N=3) n (%)	6 to <12 years (N=8) n (%)	12 to <18 years (N=20) n (%)	18 to <=21 years (N=5) n (%)
Patients with TEAEs	35 (97.2)	2 (66.7)	8 (100.0)	20 (100.0)	5 (100.0)
Patients with TEAEs Related to selpercatinib	33 (91.7)	2 (66.7)	8 (100.0)	18 (90.0)	5 (100.0)
Patients with TEAEs Maximum Severity Greater or Equal to 3	19 (52.8)	1 (33.3)	4 (50.0)	13 (65.0)	1 (20.0)
Patients with TEAEs Maximum Severity Greater or Equal to 3 and Related to selpercatinib	13 (36.1)	0 (0.0)	3 (37.5)	9 (45.0)	1 (20.0)
Patients with Serious TEAEs	15 (41.7)	1 (33.3)	3 (37.5)	10 (50.0)	1 (20.0)
Patients with Serious TEAEs and Related to selpercatinib	5 (13.9)	0 (0.0)	0 (0.0)	4 (20.0)	1 (20.0)
Patients with Fatal TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with Fatal TEAEs Related to selpercatinib	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with TEAEs and Action Taken of selpercatinib Permanently Discontinued	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
Patients with TEAEs and Action Taken of selpercatinib Permanently Discontinued and Related to selpercatinib	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DLT*a	0/4 (0.0)				
95% CI*b	(0.0, 60.2)				

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: AE = Adverse Event; CI = Confidence Interval; CTCAE = Common Terminology Criteria for Adverse Events; DLT = Dose-Limiting
Toxicity; N = number of subjects in analysis group; n = number of subjects in the specified category; TEAE = Treatment-Emergent Adverse Event.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Treatment-emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of selpercatinib.
Severity grade assignment based on CTCAE (v5.0): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening/debilitating), Grade 5 (fatal).
*a The observed DLT rate = the number of patients who experienced DLT / DLT Analysis Set subjects * 100. Multiple concurrent AEs Leading to DLT are considered as a single event.
*b Two-sided 95% exact binomial CI is presented.

Table 41. Overview of Adverse Events by Age Group and Tumour Type (Safety Analysis Set)

	Total		
	Total (N=36) n (%)	MTC (N=15) n (%)	PTC (N=15) n (%)
Patients with TEAEs	35 (97.2)	15 (100.0)	15 (100.0)
Patients with TEAEs Related to selpercatinib	33 (91.7)	15 (100.0)	15 (100.0)
Patients with TEAEs Maximum Severity Greater or Equal to 3	19 (52.8)	9 (60.0)	7 (46.7)
Patients with TEAEs Maximum Severity Greater or Equal to 3 and Related to selpercatinib	13 (36.1)	7 (46.7)	5 (33.3)
Patients with Serious TEAEs	15 (41.7)	8 (53.3)	4 (26.7)
Patients with Serious TEAEs and Related to selpercatinib	5 (13.9)	1 (6.7)	3 (20.0)

	2 to <6 years		
	Total (N=3) n (%)	MTC (N=2) n (%)	PTC (N=0) n (%)
Patients with TEAEs	2 (66.7)	2 (100.0)	0
Patients with TEAEs Related to selpercatinib	2 (66.7)	2 (100.0)	0
Patients with TEAEs Maximum Severity Greater or Equal to 3	1 (33.3)	1 (50.0)	0
Patients with TEAEs Maximum Severity Greater or Equal to 3 and Related to selpercatinib	0 (0.0)	0 (0.0)	0
Patients with Serious TEAEs	1 (33.3)	1 (50.0)	0
Patients with Serious TEAEs and Related to selpercatinib	0 (0.0)	0 (0.0)	0

Data Exported 10-Jan-2025, Visit Cutoff 08-Nov-2024
Abbreviations: AE = Adverse Event; CI = Confidence Interval; CTCAE = Common Terminology Criteria for Adverse Events; DLT = Dose-Limiting
Toxicity; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; n = number of subjects in the specified category;
PTC = Papillary Thyroid Cancer; TEAE = Treatment-Emergent Adverse Event.
The Total column includes data from subjects with Other tumor types.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Treatment-emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of selpercatinib.
Severity grade assignment based on CTCAE (v5.0): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening/debilitating), Grade 5 (fatal).
*a The observed DLT rate = the number of patients who experienced DLT / DLT Analysis Set subjects * 100. Multiple concurrent AEs Leading to DLT are considered as a single event.
*b Two-sided 95% exact binomial CI is presented.

Treatment-Emergent Adverse Events

Table 42. Treatment-Emergent Adverse Events by Maximum Grade by Decreasing Frequency Any Grade in ≥15% of Patients in any Population (Safety Analysis Set)

	Maximum Severity Patient Incidence, n (%)					
	Overall Population (N = 36)		MTC Population (N = 15)		PTC Population (N = 15)	
Preferred or *Composite* Terms	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Patients with ≥1 TEAE, n (%)	35 (97.2)	19 (52.8)	15 (100.0)	9 (60.0)	15 (100.0)	7 (46.7)
Diarrhea	17 (47.2)	1 (2.8)	5 (33.3)	0	10 (66.7)	1 (6.7)
Nausea	15 (41.7)	1 (2.8)	9 (60.0)	1 (6.7)	5 (33.3)	0
AST increased	14 (38.9)	1 (2.8)	3 (20.0)	1 (6.7)	8 (53.3)	0
Pyrexia	14 (38.9)	0	7 (46.7)	0	4 (26.7)	0
Abdominal pain	13 (36.1)	0	6 (40.)	0	4 (26.7)	0
ALT increased	12 (33.3)	3 (8.3)	4 (26.7)	1 (6.7)	5 (33.3)	1 (6.7)
Headache	12 (33.3)	0	8 (53.3)	0	4 (26.7)	0
Cough	11 (30.6)	0	6 (40.0)	0	4 (26.7)	0
Fatigue	11 (30.6)	0	5 (33.3)	0	6 (40)	0
Vomiting	11 (30.6)	3 (8.3)	9 (60.0)	3 (20.0)	2 (13.3)	0
Arthralgia	10 (27.8)	0	8 (53.3)	0	2 (13.3)	0
Corona virus infection	10 (27.8)	0	6 (40.0)	0	4 (26.7)	0
Epistaxis	10 (27.8)	0	6 (40.0)	0	2 (13.3)	0
Pain in extremity	10 (27.8)	0	7 (46.7)	0	2 (13.3)	0
Rash	10 (27.8)	0	5 (33.3)	0	3 (20.0)	0
Upper respiratory tract infection	10 (27.8)	1 (2.8)	8 (53.3)	1 (6.7)	2 (13.3)	0
Hyperphosphataemia	9 (25.0)	0	5 (33.3)	0	3 (20.0)	0
Blood alkaline phosphatase increased	8 (22.2)	0	4 (26.7)	0	2 (13.3)	0
Blood bilirubin increased	8 (22.2)	1 (2.8)	3 (20.0)	0	3 (20.0)	1 (6.7)
Constipation	8 (22.2)	2 (5.6)	5 (33.3)	2 (13.3)	2 (13.3)	0
Hypoalbuminaemia	8 (22.2)	0	7 (46.7)	0	1 (6.7)	0
Oedema	8 (22.2)	0	6 (40.0)	0	1 (6.7)	0
Oropharyngeal pain	8 (22.2)	0	4 (26.7)	0	4 (26.7)	0
Anaemia	7 (19.4)	2 (5.6)	4 (26.7)	1 (6.7)	1 (6.7)	0
Back pain	7 (19.4)	0	4 (26.7)	0	1 (6.7)	0
Blood lactate dehydrogenase increased	7 (19.4)	0	4 (26.7)	0	1 (6.7)	0
Hyperglycaemia	7 (19.4)	0	4 (26.7)	0	3 (20.0)	0
Weight increased	7 (19.4)	4 (11.1)	4 (26.7)	3 (20.0)	3 (20.0)	1 (6.7)
Hypocalcaemia	6 (16.7)	1 (2.8)	4 (26.7)	1 (6.7)	2 (13.3)	0
Rash maculo-papular	6 (16.7)	0	3 (20.0)	0	2 (13.3)	0
Sinus tachycardia	6 (16.7)	0	2 (13.3)	0	3 (20.0)	0
Urinary tract infection	6 (16.7)	1 (2.8)	4 (26.7)	1 (6.7)	1 (6.7)	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MTC = medullary thyroid cancer; n = number of patients the specified category; N = number of patients in population; PTC = papillary thyroid cancer; TEAE = treatment-emergent adverse event.
Note: Severity grade assignment based on CTCAE (v5.0).

Table 43. Treatment-Emergent Adverse Events (TEAEs) by Aggregating Composite Terms and Age Group (Safety analysis Set)

AE Category Preferred Term	Total (N=36) n (%)	2 to <6 years (N=3) n (%)	6 to <12 years (N=8) n (%)	12 to <18 years (N=20) n (%)	18 to <=21 years (N=5) n (%)
Subjects with Any TEAEs	34 (94.4)	2 (66.7)	8 (100.0)	19 (95.0)	5 (100.0)
Diarrhea	17 (47.2)	2 (66.7)	3 (37.5)	9 (45.0)	3 (60.0)
Diarrhoea	17 (47.2)	2 (66.7)	3 (37.5)	9 (45.0)	3 (60.0)
Anal incontinence	1 (2.8)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	14 (38.9)	0 (0.0)	7 (87.5)	6 (30.0)	1 (20.0)
Aspartate aminotransferase increased	14 (38.9)	0 (0.0)	7 (87.5)	6 (30.0)	1 (20.0)
Pyrexia	14 (38.9)	2 (66.7)	4 (50.0)	8 (40.0)	0 (0.0)
Pyrexia	14 (38.9)	2 (66.7)	4 (50.0)	8 (40.0)	0 (0.0)
Abdominal Pain	13 (36.1)	0 (0.0)	4 (50.0)	7 (35.0)	2 (40.0)
Abdominal pain	12 (33.3)	0 (0.0)	4 (50.0)	6 (30.0)	2 (40.0)
Abdominal pain upper	2 (5.6)	0 (0.0)	0 (0.0)	1 (5.0)	1 (20.0)
Abdominal discomfort	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Alanine aminotransferase increased	12 (33.3)	0 (0.0)	6 (75.0)	5 (25.0)	1 (20.0)
Alanine aminotransferase increased	12 (33.3)	0 (0.0)	6 (75.0)	5 (25.0)	1 (20.0)
Headache	12 (33.3)	1 (33.3)	3 (37.5)	6 (30.0)	2 (40.0)
Headache	12 (33.3)	1 (33.3)	3 (37.5)	6 (30.0)	2 (40.0)
Cough	11 (30.6)	1 (33.3)	3 (37.5)	5 (25.0)	2 (40.0)
Cough	11 (30.6)	1 (33.3)	3 (37.5)	5 (25.0)	2 (40.0)
Fatigue	11 (30.6)	0 (0.0)	0 (0.0)	10 (50.0)	1 (20.0)
Fatigue	8 (22.2)	0 (0.0)	0 (0.0)	7 (35.0)	1 (20.0)
Asthenia	3 (8.3)	0 (0.0)	0 (0.0)	3 (15.0)	0 (0.0)
Malaise	2 (5.6)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
Vomiting	11 (30.6)	2 (66.7)	3 (37.5)	5 (25.0)	1 (20.0)
Vomiting	11 (30.6)	2 (66.7)	3 (37.5)	5 (25.0)	1 (20.0)
Rash	10 (27.8)	2 (66.7)	3 (37.5)	5 (25.0)	0 (0.0)
Rash maculo-papular	6 (16.7)	1 (33.3)	3 (37.5)	2 (10.0)	0 (0.0)
Rash	4 (11.1)	0 (0.0)	1 (12.5)	3 (15.0)	0 (0.0)
Rash erythematous	1 (2.8)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Urticaria	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Constipation	8 (22.2)	1 (33.3)	1 (12.5)	5 (25.0)	1 (20.0)
Constipation	8 (22.2)	1 (33.3)	1 (12.5)	5 (25.0)	1 (20.0)
Oedema	8 (22.2)	1 (33.3)	3 (37.5)	4 (20.0)	0 (0.0)
Face oedema	6 (16.7)	0 (0.0)	2 (25.0)	4 (20.0)	0 (0.0)
Oedema peripheral	2 (5.6)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
Periorbital oedema	2 (5.6)	0 (0.0)	2 (25.0)	0 (0.0)	0 (0.0)
Generalised oedema	1 (2.8)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Localised oedema	1 (2.8)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Swelling	1 (2.8)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Blood creatinine increased	5 (13.9)	0 (0.0)	1 (12.5)	3 (15.0)	1 (20.0)
Blood creatinine increased	5 (13.9)	0 (0.0)	1 (12.5)	3 (15.0)	1 (20.0)
Dizziness	5 (13.9)	0 (0.0)	0 (0.0)	5 (25.0)	0 (0.0)
Dizziness	5 (13.9)	0 (0.0)	0 (0.0)	5 (25.0)	0 (0.0)
Electrocardiogram QT prolonged	5 (13.9)	0 (0.0)	2 (25.0)	3 (15.0)	0 (0.0)
Electrocardiogram QT prolonged	4 (11.1)	0 (0.0)	2 (25.0)	2 (10.0)	0 (0.0)
Electrocardiogram QRS complex prolonged	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Hypersensitivity	4 (11.1)	0 (0.0)	0 (0.0)	4 (20.0)	0 (0.0)
Drug hypersensitivity	2 (5.6)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
Hypersensitivity	2 (5.6)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
Decreased appetite	3 (8.3)	0 (0.0)	0 (0.0)	2 (10.0)	1 (20.0)
Decreased appetite	3 (8.3)	0 (0.0)	0 (0.0)	2 (10.0)	1 (20.0)
Dyspnea	3 (8.3)	1 (33.3)	1 (12.5)	1 (5.0)	0 (0.0)
Dyspnoea	3 (8.3)	1 (33.3)	1 (12.5)	1 (5.0)	0 (0.0)
Hypertension	3 (8.3)	0 (0.0)	0 (0.0)	2 (10.0)	1 (20.0)
Hypertension	3 (8.3)	0 (0.0)	0 (0.0)	2 (10.0)	1 (20.0)
Dry Mouth	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Dry mouth	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Thrombocytopenia	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Platelet count decreased	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)

Data Exported 10-Jan-2025, Visit Cutoff 08-Nov-2024
Abbreviations: AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in analysis group; n = number of subjects in the specified category; TEAE = Treatment-Emergent Adverse Event.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Treatment-emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of selpercatinib.
If a subject experienced more than one adverse event within a preferred term, the subject is counted once in that preferred term.
If a subject experienced more than one adverse event within an AE category, the subject is counted once in that AE category.
Reported adverse event terms were coded using MedDRA (version 21.1 or later).
TEAEs are sorted in decreasing order of frequency based on Overall Safety Analysis Set.

Grade 3 or greater TEAEs

In the Overall Population, a total of 19 patients (52.8%) had Grade 3 or greater TEAEs, of which

- 17 patients (47.2%) had Grade 3 TEAEs
- 2 patients (5.6%) had Grade 4 TEAEs (blood creatine phosphokinase increased and foetal death), and
- no patients had Grade 5 (fatal) TEAEs.

Table 44. Treatment-Emergent Adverse Events Grade ≥3 Occurring in ≥2 Patients in any Population (Safety Analysis Set)

Preferred or *Composite* Terms	Grade ≥3 n (%)		
	Overall Population (N = 36)	MTC Population (N = 15)	PTC Population (N = 15)
Patients with TEAEs			
Weight increased	4 (11.1)	3 (20.0)	1 (6.7)
ALT increased	3 (8.3)	1 (6.7)	1 (6.7)
Vomiting	3 (8.3)	3 (20.0)	0 (0.0)
Anaemia	2 (5.6)	1 (6.7)	0 (0.0)
Constipation	2 (5.6)	2 (13.3)	0 (0.0)
Hypertension	2 (5.6)	0 (0.0)	1 (6.7)
Hypokalaemia	2 (5.6)	2 (13.3)	0 (0.0)
Neutrophil count decreased	2 (5.6)	0 (0.0)	2 (13.3)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MTC = medullary thyroid cancer; n = number of patients in the specific category; N = number of patients in population; PTC = papillary thyroid cancer; TEAE = treatment-emergent adverse event.
Note: Severity grade assignment based on CTCAE (v5.0).
Data cutoff date: 08 November 2024

Treatment-Emergent Adverse Events Related to Selpercatinib

Table 45. Drug-Related Treatment-Emergent Adverse Events (TEAEs) by Tumour Type by Maximum Grade by Decreasing Frequency Any Grade in ≥15% of Patients in any Population (Safety Analysis Set)

Preferred Term	Total (N=36) n (%)	MTC (N=15) n (%)	PTC (N=15) n (%)	Other (N=6) n (%)
Subjects with Any Drug-Related TEAEs	33 (91.7)	15 (100.0)	15 (100.0)	3 (50.0)
Aspartate aminotransferase increased	13 (36.1)	3 (20.0)	7 (46.7)	3 (50.0)
Alanine aminotransferase increased	12 (33.3)	4 (26.7)	5 (33.3)	3 (50.0)
Diarrhoea	10 (27.8)	2 (13.3)	6 (40.0)	2 (33.3)
Blood bilirubin increased	8 (22.2)	3 (20.0)	3 (20.0)	2 (33.3)
Blood alkaline phosphatase increased	7 (19.4)	3 (20.0)	2 (13.3)	2 (33.3)
Fatigue	7 (19.4)	3 (20.0)	4 (26.7)	0 (0.0)
Hyperphosphataemia	7 (19.4)	5 (33.3)	1 (6.7)	1 (16.7)
Headache	6 (16.7)	3 (20.0)	3 (20.0)	0 (0.0)
Hypoalbuminaemia	6 (16.7)	5 (33.3)	1 (6.7)	0 (0.0)
Weight increased	6 (16.7)	4 (26.7)	2 (13.3)	0 (0.0)
Abdominal pain	5 (13.9)	1 (6.7)	2 (13.3)	2 (33.3)
Anaemia	5 (13.9)	4 (26.7)	1 (6.7)	0 (0.0)
Blood lactate dehydrogenase increased	5 (13.9)	4 (26.7)	1 (6.7)	0 (0.0)
Nausea	5 (13.9)	2 (13.3)	3 (20.0)	0 (0.0)
Ascites	4 (11.1)	0 (0.0)	4 (26.7)	0 (0.0)
Blood creatinine increased	4 (11.1)	1 (6.7)	3 (20.0)	0 (0.0)
Electrocardiogram QT prolonged	4 (11.1)	2 (13.3)	1 (6.7)	1 (16.7)
Face oedema	4 (11.1)	3 (20.0)	1 (6.7)	0 (0.0)
Hyperkalaemia	4 (11.1)	3 (20.0)	0 (0.0)	1 (16.7)
Blood thyroid stimulating hormone increased	3 (8.3)	3 (20.0)	0 (0.0)	0 (0.0)
Constipation	3 (8.3)	2 (13.3)	1 (6.7)	0 (0.0)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; n = number of subjects in the specified category; PTC = Papillary Thyroid Cancer; TEAE = Treatment-Emergent Adverse Event.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Treatment-emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of selpercatinib.
If a subject experienced more than one adverse event within a preferred term, the subject is counted once in that preferred term.
Reported adverse event terms were coded using MedDRA (version 21.1 or later).
TEAEs are sorted in decreasing order of frequency based on Overall Safety Analysis Set.

Table 46. Drug-Related Treatment-emergent Adverse Events (TEAEs) by Preferred Term and Age Group (Safety Analysis Set)

Preferred Term	Total (N=36) n (%)	2 to <6 years (N=3) n (%)	6 to <12 years (N=8) n (%)	12 to <18 years (N=20) n (%)	18 to <=21 years (N=5) n (%)
Subjects with Any Drug-Related TEAEs	33 (91.7)	2 (66.7)	8 (100.0)	18 (90.0)	5 (100.0)
Aspartate aminotransferase increased	13 (36.1)	0 (0.0)	7 (87.5)	5 (25.0)	1 (20.0)
Alanine aminotransferase increased	12 (33.3)	0 (0.0)	6 (75.0)	5 (25.0)	1 (20.0)
Diarrhoea	10 (27.8)	0 (0.0)	2 (25.0)	6 (30.0)	2 (40.0)
Blood bilirubin increased	8 (22.2)	0 (0.0)	3 (37.5)	3 (15.0)	2 (40.0)
Blood alkaline phosphatase increased	7 (19.4)	0 (0.0)	3 (37.5)	4 (20.0)	0 (0.0)
Fatigue	7 (19.4)	0 (0.0)	0 (0.0)	6 (30.0)	1 (20.0)
Hyperphosphataemia	7 (19.4)	0 (0.0)	3 (37.5)	2 (10.0)	2 (40.0)
Headache	6 (16.7)	0 (0.0)	1 (12.5)	4 (20.0)	1 (20.0)
Hypoalbuminaemia	6 (16.7)	0 (0.0)	3 (37.5)	3 (15.0)	0 (0.0)
Weight increased	6 (16.7)	0 (0.0)	2 (25.0)	4 (20.0)	0 (0.0)
Abdominal pain	5 (13.9)	0 (0.0)	3 (37.5)	2 (10.0)	0 (0.0)
Anaemia	5 (13.9)	0 (0.0)	3 (37.5)	2 (10.0)	0 (0.0)
Blood lactate dehydrogenase increased	5 (13.9)	0 (0.0)	2 (25.0)	2 (10.0)	1 (20.0)
Nausea	5 (13.9)	0 (0.0)	0 (0.0)	4 (20.0)	1 (20.0)
Ascites	4 (11.1)	0 (0.0)	0 (0.0)	3 (15.0)	1 (20.0)
Blood creatinine increased	4 (11.1)	0 (0.0)	0 (0.0)	3 (15.0)	1 (20.0)
Electrocardiogram QT prolonged	4 (11.1)	0 (0.0)	2 (25.0)	2 (10.0)	0 (0.0)
Face oedema	4 (11.1)	0 (0.0)	1 (12.5)	3 (15.0)	0 (0.0)
Hyperkalaemia	4 (11.1)	0 (0.0)	2 (25.0)	1 (5.0)	1 (20.0)
Blood thyroid stimulating hormone increased	3 (8.3)	0 (0.0)	2 (25.0)	1 (5.0)	0 (0.0)
Constipation	3 (8.3)	1 (33.3)	0 (0.0)	1 (5.0)	1 (20.0)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in analysis group; n = number of subjects in the specified category; TEAE = Treatment-Emergent Adverse Event.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Treatment-emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of selpercatinib.
If a subject experienced more than one adverse event within a preferred term, the subject is counted once in that preferred term.
Reported adverse event terms were coded using MedDRA (version 21.1 or later).
TEAEs are sorted in decreasing order of frequency based on Overall Safety Analysis Set.

Table 47. Drug-Related Treatment-emergent Adverse Events (TEAEs) by System Organ Class, Grade, and Age Group (Safety Analysis Set)

System Organ Class Preferred Term	Total (N=36)		2 to <6 years (N=3)		6 to <12 years (N=8)	
	Any Grade n (%)	Grade 3/4/5 n (%)	Any Grade n (%)	Grade 3/4/5 n (%)	Any Grade n (%)	Grade 3/4/5 n (%)
Any Drug-Related TEAEs	33 (91.7)	13 (36.1)	2 (66.7)	0 (0.0)	8 (100.0)	3 (37.5)
Investigations	25 (69.4)	10 (27.8)	0 (0.0)	0 (0.0)	8 (100.0)	3 (37.5)
Aspartate aminotransferase increased	13 (36.1)	1 (2.8)	0 (0.0)	0 (0.0)	7 (87.5)	1 (12.5)
Alanine aminotransferase increased	12 (33.3)	3 (8.3)	0 (0.0)	0 (0.0)	6 (75.0)	2 (25.0)
Blood bilirubin increased	8 (22.2)	1 (2.8)	0 (0.0)	0 (0.0)	3 (37.5)	0 (0.0)
Blood alkaline phosphatase increased	7 (19.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (37.5)	0 (0.0)
Weight increased	6 (16.7)	3 (8.3)	0 (0.0)	0 (0.0)	2 (25.0)	1 (12.5)
Blood lactate dehydrogenase increased	5 (13.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
Blood creatinine increased	4 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram QT prolonged	4 (11.1)	1 (2.8)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
Blood thyroid stimulating hormone increased	3 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
Neutrophil count decreased	3 (8.3)	2 (5.6)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
Blood bicarbonate decreased	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
Gamma-glutamyltransferase increased	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
Lipase increased	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)

System Organ Class Preferred Term	12 to <18 years (N=20)		18 to <=21 years (N=5)	
	Any Grade n (%)	Grade 3/4/5 n (%)	Any Grade n (%)	Grade 3/4/5 n (%)
Any Drug-Related TEAEs	18 (90.0)	9 (45.0)	5 (100.0)	1 (20.0)
Investigations	13 (65.0)	7 (35.0)	4 (80.0)	0 (0.0)
Aspartate aminotransferase increased	5 (25.0)	0 (0.0)	1 (20.0)	0 (0.0)
Alanine aminotransferase increased	5 (25.0)	1 (5.0)	1 (20.0)	0 (0.0)
Blood bilirubin increased	3 (15.0)	1 (5.0)	2 (40.0)	0 (0.0)
Blood alkaline phosphatase increased	4 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight increased	4 (20.0)	2 (10.0)	0 (0.0)	0 (0.0)
Blood lactate dehydrogenase increased	2 (10.0)	0 (0.0)	1 (20.0)	0 (0.0)
Blood creatinine increased	3 (15.0)	0 (0.0)	1 (20.0)	0 (0.0)
Electrocardiogram QT prolonged	2 (10.0)	1 (5.0)	0 (0.0)	0 (0.0)
Blood thyroid stimulating hormone increased	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophil count decreased	2 (10.0)	2 (10.0)	0 (0.0)	0 (0.0)
Blood bicarbonate decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gamma-glutamyltransferase increased	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lipase increased	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in analysis group; n = number of subjects in the specified category; TEAE = Treatment-Emergent Adverse Event.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Treatment-emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of selpercatinib.
If a subject experienced more than one adverse event within a preferred term, the subject is counted once in that preferred term.
If a subject experienced more than one adverse event within a system organ class, the subject is counted once in that system organ class.
Reported adverse event terms were coded using MedDRA (version 21.1 or later).
Severity grade assignment based on CTCAE (v5.0): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening/debilitating), Grade 5 (fatal).
TEAEs are sorted in decreasing order of frequency based on Overall Safety Analysis Set.

Table 48. Grade 3, 4, or 5 Drug-Related Treatment-Emergent Adverse Events (TEAEs) by preferred Term and Age Group (Safety Analysis Set)

Preferred Term	Total (N=36) n (%)	2 to <6 years (N=3) n (%)	6 to <12 years (N=8) n (%)	12 to <18 years (N=20) n (%)	18 to <=21 years (N=5) n (%)
Subjects with Any Grade 3/4/5 Drug-Related TEAEs	13 (36.1)	0 (0.0)	3 (37.5)	9 (45.0)	1 (20.0)
Alanine aminotransferase increased	3 (8.3)	0 (0.0)	2 (25.0)	1 (5.0)	0 (0.0)
Weight increased	3 (8.3)	0 (0.0)	1 (12.5)	2 (10.0)	0 (0.0)
Neutrophil count decreased	2 (5.6)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
Aspartate aminotransferase increased	1 (2.8)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Blood bilirubin increased	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Drug hypersensitivity	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Electrocardiogram QT prolonged	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Erectile dysfunction	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Foetal death	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
Gastrointestinal fistula	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Hypocalcaemia	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Wound dehiscence	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Wound infection	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in analysis group; n = number of subjects in the specified category; TEAE = Treatment-Emergent Adverse Event.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Treatment-emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of selpercatinib.
If a subject experienced more than one adverse event within a preferred term, the subject is counted once in that preferred term.
Reported adverse event terms were coded using MedDRA (version 21.1 or later).
Severity grade assignment based on CTCAE (v5.0): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening/ debilitating), Grade 5 (fatal).
TEAEs are sorted in decreasing order of frequency based on Overall Safety Analysis Set.

Table 49. Drug-Related Treatment-emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term, Maximum Severity, and Tumour Type (Safety Analysis Set)

Tumor Type / System Organ Class / Preferred Term	Maximum Severity (n, %) Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Missing	Total
Total (N=36)							
Maximum Severity Grade	6 (16.7)	14 (38.9)	12 (33.3)	1 (2.8)	0 (0.0)	0 (0.0)	33 (91.7)
Investigations	7 (19.4)	8 (22.2)	10 (27.8)	0 (0.0)	0 (0.0)	0 (0.0)	25 (69.4)
Aspartate aminotransferase increased	10 (27.8)	2 (5.6)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	13 (36.1)
Alanine aminotransferase increased	9 (25.0)	0 (0.0)	3 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	12 (33.3)
Blood bilirubin increased	2 (5.6)	5 (13.9)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	8 (22.2)
Blood alkaline phosphatase increased	6 (16.7)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (19.4)
Weight increased	1 (2.8)	2 (5.6)	3 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (16.7)
Blood lactate dehydrogenase increased	5 (13.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (13.9)
Blood creatinine increased	3 (8.3)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (11.1)
Electrocardiogram QT prolonged	3 (8.3)	0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (11.1)
Blood thyroid stimulating hormone increased	3 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (8.3)
Neutrophil count decreased	0 (0.0)	1 (2.8)	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (8.3)
Blood bicarbonate decreased	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.6)
Gamma-glutamyltransferase increased	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.6)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; n = number of subjects in the specified category; PTC = Papillary Thyroid Cancer; TEAE = Treatment-Emergent Adverse Event.
Percentage is calculated based on the number of patients in the corresponding analysis set (N) as the denominator.
Treatment-emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of selpercatinib.
Patients with multiple severity ratings for a given adverse event are counted once under the maximum severity.
Reported adverse event terms were coded using MedDRA (version 21.1 or later).
Severity grade assignment based on CTCAE (v5.0): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening/ debilitating), Grade 5 (fatal).

Table 50. Treatment-Emergent Adverse Events by Maximum Grade by Decreasing Frequency Any Grade in ≥15% of Patients in Any Population (Safety Analysis Set)

	Maximum Severity Patient Incidence, n (%)							
	Overall Population (N=36)		**MTC Population (N=15)**		**PTC Population (N=15)**		**Other Solid Tumours (N=6)**	
Preferred or *Composite* Terms	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Patients with ≥1 TEAE, n (%)	35 (97.2)	19 (52.8)	15 (100.0)	9 (60.0)	15 (100.0)	7 (46.7)	5 (83.3)	3 (50.0)

Diarrhea	17 (47.2)	1 (2.8)	5 (33.3)	0	10 (66.7)	1 (6.7)	2 (33.3)	0
Nausea	15 (41.7)	1 (2.8)	9 (60.0)	1 (6.7)	5 (33.3)	0	1 (16.7)	0
AST increased	14 (38.9)	1 (2.8)	3 (20.0)	1 (6.7)	8 (53.3)	0	3 (50.0)	0
Pyrexia	14 (38.9)	0	7 (46.7)	0	4 (26.7)	0	3 (50.0)	0
Abdominal pain	13 (36.1)	0	6 (40.)	0	4 (26.7)	0	3 (50.0)	0
ALT increased	12 (33.3)	3 (8.3)	4 (26.7)	1 (6.7)	5 (33.3)	1 (6.7)	3 (50.0)	1 (16.7)
Headache	12 (33.3)	0	8 (53.3)	0	4 (26.7)	0	0	0
Cough	11 (30.6)	0	6 (40.0)	0	4 (26.7)	0	1 (16.7)	0
Fatigue	11 (30.6)	0	5 (33.3)	0	6 (40)	0	0	0
Vomiting	11 (30.6)	3 (8.3)	9 (60.0)	3 (20.0)	2 (13.3)	0	0	0
Arthralgia	10 (27.8)	0	8 (53.3)	0	2 (13.3)	0	0	0
Corona virus infection	10 (27.8)	0	6 (40.0)	0	4 (26.7)	0	0	0
Epistaxis	10 (27.8)	0	6 (40.0)	0	2 (13.3)	0	2 (33.3)	0
Pain in extremity	10 (27.8)	0	7 (46.7)	0	2 (13.3)	0	1 (16.7)	0
Rash	10 (27.8)	0	5 (33.3)	0	3 (20.0)	0	2 (33.3)	0
Upper respiratory tract infection	10 (27.8)	1 (2.8)	8 (53.3)	1 (6.7)	2 (13.3)	0	0	0
Hyperphosphataemia	9 (25.0)	0	5 (33.3)	0	3 (20.0)	0	1 (16.7)	0
Blood alkaline phosphatase increased	8 (22.2)	0	4 (26.7)	0	2 (13.3)	0	2 (33.3)	0
Blood bilirubin increased	8 (22.2)	1 (2.8)	3 (20.0)	0	3 (20.0)	1 (6.7)	2 (33.3)	0
Constipation	8 (22.2)	2 (5.6)	5 (33.3)	2 (13.3)	2 (13.3)	0	1 (16.7)	0
Hypoalbuminaemia	8 (22.2)	0	7 (46.7)	0	1 (6.7)	0	0	0
Oedema	8 (22.2)	0	6 (40.0)	0	1 (6.7)	0	1 (16.7)	0
Oropharyngeal pain	8 (22.2)	0	4 (26.7)	0	4 (26.7)	0	0	0
Anaemia	7 (19.4)	2 (5.6)	4 (26.7)	1 (6.7)	1 (6.7)	0	2 (33.3)	1 (16.7)
Back pain	7 (19.4)	0	4 (26.7)	0	1 (6.7)	0	2 (33.3)	0
Blood lactate dehydrogenase increased	7 (19.4)	0	4 (26.7)	0	1 (6.7)	0	2 (33.3)	0
Hyperglycaemia	7 (19.4)	0	4 (26.7)	0	3 (20.0)	0	0	0
Weight increased	7 (19.4)	4 (11.1)	4 (26.7)	3 (20.0)	3 (20.0)	1 (6.7)	0	0
Hypocalcaemia	6 (16.7)	1 (2.8)	4 (26.7)	1 (6.7)	2 (13.3)	0	0	0
Rash maculo-papular	6 (16.7)	0	3 (20.0)	0	2 (13.3)	0	1 (16.7)	0
Sinus tachycardia	6 (16.7)	0	2 (13.3)	0	3 (20.0)	0	1 (16.7)	0
Urinary tract infection	6 (16.7)	1 (2.8)	4 (26.7)	1 (6.7)	1 (6.7)	0	1 (16.7)	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; MTC = medullary thyroid cancer; n = number of patients the specified category; N = number of patients in population; PTC = papillary thyroid cancer; TEAE = treatment-emergent adverse event.

Note: Severity grade assignment based on CTCAE (v5.0).

Serious adverse event/deaths/other significant events

Serious Treatment-Emergent Adverse Events (TE-SAEs)

In the **Overall Population**, a total of **15 patients (41.7%) experienced any-grade TE-SAEs**. Of the TE-SAEs reported, vomiting was reported as 2 events, while all other TE-SAEs had a single occurrence.

One Grade 4 TE-SAE occurred in the study (fetal death). A positive pregnancy test was reported in 1 patient greater than 18 years of age at the time of the AE. In accordance with protocol, the patient was immediately withdrawn from the study following positive pregnancy test results. Subsequent follow-up revealed that the patient experienced loss of pregnancy at 8 weeks of gestation, which was considered as medically significant by the study investigator.

No Grade 5 TE-SAE occurred in the study.

6 TE-SAEs were considered to be treatment-related by the investigator (**ascites, foetal death, drug hypersensitivity, gastrointestinal fistula, wound infection, blood bilirubin increased**), and no patients discontinued the study treatment due to TE-SAEs.

Table 51. Treatment-Emergent Serious Adverse Events (TE-SAEs) by Preferred Term and Tumour Type (Safety Analysis Set)

Preferred Term	Total (N=36) n (%)	MTC (N=15) n (%)	PTC (N=15) n (%)	Other (N=6) n (%)
Subjects with Any TESAEs	15 (41.7)	8 (53.3)	4 (26.7)	3 (50.0)
Vomiting	2 (5.6)	2 (13.3)	0 (0.0)	0 (0.0)
Abdominal infection	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Abdominal pain	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Ascites	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
Aspiration	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Blood bilirubin increased	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
Constipation	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Diarrhoea	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Drug hypersensitivity	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Epiphysiolysis	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Febrile neutropenia	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Fibroadenoma of breast	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
Foetal death	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
Gastrointestinal fistula	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Haemoptysis	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Nausea	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Pneumatosis intestinalis	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Pneumonia	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Rhinovirus infection	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Sepsis	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis
group; n = number of subjects in the specified category; PTC = Papillary Thyroid Cancer; TEAE = Treatment-Emergent Adverse Event; TESAE = Treatment-Emergent Serious Adverse Event.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Treatment-emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of selpercatinib.
If a subject experienced more than one adverse event within a preferred term, the subject is counted once in that preferred term.
Reported adverse event terms were coded using MedDRA (version 21.1 or later).
TESAEs are sorted in decreasing order of frequency based on Overall Safety Analysis Set.

Deaths

In total, 4 deaths (11.1%) were reported during the study. All these deaths were reported in the Other Solid Tumours Population and were the result of disease progression. No deaths were attributed to TEAEs. Of the 4 deaths, 1 death was reported within 28 days of the last dose of selpercatinib while 3 deaths occurred more than 28 days after the last dose of selpercatinib. All deaths were considered related to disease progression.

Adverse Events of Special Interest

Based upon considerations of preclinical toxicology and safety trends observed during the conduct of the selpercatinib LIBRETTO-001 study, the following event categories were deemed AESIs:

- **liver injury**
- **hypertension**
- **drug hypersensitivity, and**
- **QT prolongation**.

Liver injury

ALT Increased

Most events of ALT increased were Grade 1 (25.0%) in severity in the Overall Population with no Grade 4 or 5 events reported across populations. No TE-SAEs or drug discontinuations were reported. Three patients (8.3%) had TEAEs leading to dose interruptions and 3 patients (8.3%) had TEAEs leading to dose reductions due to ALT.

AST increased

Most events of AST increased were Grade 1 (30.6%) in severity in the Overall Population with no Grade 4 or 5 events reported across populations. No TE-SAEs, dose reductions or discontinuations were reported. Three patients (8.3%) had TEAEs leading to dose interruptions due to AST increased.

Drug-related hepatic disorders based on SMQ

Analysis of events related to liver injury was performed based on the drug-related hepatic disorders-comprehensive search [SMQ]. **The majority of the TEAEs identified based on drug-related hepatic disorders SMQ were of low severity (Grade 1 or 2). TEAEs were well managed in most patients by dose interruptions (19.4%) or dose reductions (11.1%).** No treatment discontinuations were observed. The evaluation of this broad SMQ did not identify anything of clinical significance and was consistent with the AESI liver injury.

Additionally, the evaluation of drug-related hepatic disorders SMQ did not identify anything of clinical significance and was consistent with the AESI of liver injury. TEAEs identified based on drug related hepatic disorders were well managed in most patients by dose interruptions (19.4%) or dose reductions (11.1%). No treatment discontinuations were observed.

Hypertension

The AESI of hypertension was reviewed based on AE terms: PTs of "Hypertension", "Blood Pressure Abnormal", and "Blood Pressure Increased." Of the 36 patients, any-grade hypertension was reported in 3 (8.3%) patients. Of which,

- 2 (5.6%) patients had Grade 3 in severity, and
- no TE-SAE, drug interruption, reduction, or discontinuation were observed.

The low frequency of AESI hypertension is consistent with expectations given the younger age of the patients in LIBRETTO-121. Of these 3 patients, 2 were aged 12 to <18 years and 1 was aged 18 to 21 years. No TE-SAE, drug interruption, reduction, or discontinuations were observed.

Hypersensitivity

Of the 36 patients, any-grade hypersensitivity was reported in 4 (11.1%) patients and were of Grade 1 to Grade 3 in severity. However, no drug reductions or discontinuations were observed.

Electrocardiogram QT interval prolongation

Of the 36 patients, electrocardiogram QT prolongation was reported in 5 (13.9%) patients and the majority were of Grade 1 in severity with 1 patient reporting Grade 3 severity and no Grade 4 or 5 events reported. No TE-SAE, drug discontinuations, or dose reductions were observed. One TEAE led to dose interruption.

Other Significant AEs

To fully evaluate the safety profile of selpercatinib, all events that are included as warnings or precautions in the SmPC or are requested to be closely monitored by the Pharmacovigilance Risk Assessment Committee and which are not already included in the AESI list (below) were also assessed.

Overall, an evaluation of the following AEs from across the tumour types and age groups did not identify any clinically significant differences compared with the Overall Population.

Slipped Upper Femoral Epiphysis/ Slipped Capital Femoral Epiphysis (SCFE/SUFE) was previously added as an adverse drug reaction for pediatric and adolescent patients treated with selpercatinib. The number of TEAEs related to SUFE/SCFE (n = 1) remains unchanged since the previous data cut, and no additional TEAEs of SCFE/SUFE were reported in this data analysis for LIBRETTO-121.

No events were reported in the Overall Population regarding *Interstitial lung disease/pneumonitis* (SMQ) and *Tumour lysis syndrome* (SMQ).

Haemorrhage (SMQ)

TEAEs from the *Haemorrhages* (SMQ) were reported in 14 (38.9%) patients in the Overall Population. The most frequently reported TEAEs in the *Haemorrhage* (SMQ) were *Epistaxis* (27.8%, n=10) and *Haematuria* (5.6%, n=2).

TEAEs from the *Haemorrhages* (SMQ) in the Overall Population

- were considered related to selpercatinib for 4 (11.1%) patients
- were mostly Grade 1 (30.6%) with no Grade 3 or greater events reported; 1 event (*Haemoptysis*) was serious but deemed not related to selpercatinib, and
- no events led to dose modifications, interruptions, or discontinuations.

Hypothyroidism (SMQ)

TEAEs from the *Hypothyroidism* (SMQ) were reported in 8 (22.2%) patients in the Overall Population.

TEAEs from the *Hypothyroidism* (SMQ) in the Overall Population

- were considered related to selpercatinib for 6 (16.7%) patients
- all events were Grade 1 or 2 in severity
- no events were serious, and
- no events led to dose modifications, interruptions, or discontinuations.

Impaired wound healing

TEAEs from the *Impaired wound healing* (SMQ) were reported in 2 (5.6%) patients in the Overall Population.

The only TEAE from the *Impaired wound healing* (SMQ) in the Overall Population was wound dehiscence, which

- was considered related to selpercatinib in 1 patient
- the 2 events were Grade 2 and Grade 3 in severity
- no events were serious, and
- one event led to dose interruption while no events led to dose reductions or discontinuations.

Embryo-foetal toxicity

As of the data cut-off, the frequency of embryo-foetal toxicity remains consistent with the previous interim analysis data cut-off date (13 January 2023). A positive pregnancy test was reported in 1 patient greater than 18 years of age at the time of the AE. In accordance with the protocol, the patient was immediately withdrawn from the study following the positive pregnancy test result. Subsequent follow-up revealed that the patient experienced loss of pregnancy at 8 weeks of gestation, which was considered as medically significant by the study investigator.

Other significant AEs conclusion

Most of the Other Significant AEs (listed above) in this study were low grade (Grade 1 or Grade 2), did not lead to dose modification or permanent discontinuation, and were generally consistent with the known safety profile of selpercatinib. No clinically significant differences were observed between the MTC, PTC, and Other Solid Tumours Populations when compared with the Overall Population.

Other Safety Evaluations

Growth Plate Evaluation

Along with general monitoring activities for treatment with selpercatinib, the potential for growth plate abnormalities was monitored based on preclinical findings. As of the data cutoff date, 35 of the 36 patients treated were assessed at baseline for the need for growth plate monitoring (excluding the patient with osteosarcoma). **Of these 35 patients, the growth plate was open at baseline in 33 patients. Apart from the previously reported case of SCFE/SUFE, a recognised adverse drug reaction, no other AEs related to early growth plate closure were reported in patients undergoing monitoring**.

An interactive boxplot for growth evaluation was provided by the applicant (not shown). Observed and mean change in Z-scores and percentile for body mass index, weight, and height were plotted over time. **No clinically significant differences were noted in the growth plate based on the weight, height, or body mass index across the age groups.**

Dental Evaluation

Of the 36 patients treated, 15 patients who were at least 5 years of age did not have full set of permanent teeth. Of the 15 patients, 5 had changes in tooth development. AEs included one each of dental caries and dental operation (tooth extraction and upper frenectomy), both were assessed as not related to the study drug by the investigator.

Pubertal Maturation

Of the 36 patients treated, 14 patients who were at least 7 years of age were evaluated for pubertal maturation per protocol. Pubertal status was assessed by Tanner staging at screening, followed by every 6 months until pubertal maturity (males and females) and by date of menarche

(females). One patient entered the study with pre-existing pubertal delay. The assessment showed that there were no delays in sexual maturity that developed during the study in patients aged at least 7 years.

Vital Signs

Vital sign assessments included blood pressure, height, and body weight. Abnormal findings in blood pressure are considered as AESIs. In body weight assessments, no clinically meaningful change from baseline was observed.

Electrocardiograms

The following observations were made in the Overall Population:

- At baseline, all patients had a QTcF of not more than 450 msec. Maximum QTcF increase was more than 60 msec from baseline in 11 patients (30.6%) and 2 (5.6%) patients had maximum QTcF in the range greater than 480 to 500 msec.
- At the last postbaseline value, 2 (5.6%) patients had QTcF increased more than 60 msec and 1 patient had maximum QTcF in the range greater than 480 to 500 msec from baseline.
- Furthermore, there were no observed maximum postbaseline or last postbaseline QTcF greater than 500 msec in the study.

Adverse Drug Reactions

The frequency of previously identified ADRs for selpercatinib observed in LIBRETTO-121 is provided:

Table 52. Adverse Drug Reactions in Patients Receiving Selpercatinib in LIBRETTO-121

	Selpercatinib N=36	
Event	**All Grades n (%)**	**Grade ≥3 n (%)**
Renal and urinary tract infections[a]	7 (19.4)	1 (2.8)
Pneumonia[a]	1 (2.8)	1 (2.8)
Hypersensitivity[b]	4 (11.1)	1 (2.8)
Hypothyroidism[c]	8 (22.2)	0 (0.0)
Decreased appetite	3 (8.3)	0 (0.0)
Headache	12 (33.3)	0 (0.0)
Dizziness	5 (13.9)	0 (0.0)
Electrocardiogram QT prolonged[b]	5 (13.9)	1 (2.8)
Hypertension	3 (8.3)	2 (5.6)

Haemorrhage[c]	14 (38.9)	0 (0.0)
Interstitial lung disease/pneumonitis	0 (0.0)	0 (0.0)
Chylothorax	0 (0.0)	0 (0.0)
Diarrhoea[b]	17 (47.2)	1 (2.8)
Dry mouth	1 (2.8)	0 (0.0)
Abdominal pain[b]	13 (36.1)	0 (0.0)
Constipation	8 (22.2)	2 (5.6)
Nausea	15 (41.7)	1 (2.8)
Vomiting	11 (30.6)	3 (8.3)
Stomatitis	4 (11.1)	0 (0.0)
Chylous ascites	1 (2.8)	0 (0.0)
Rash[b]	10 (27.8)	0 (0.0)
Epiphysiolysis of the femoral head	1 (2.8)	1 (2.8)
Erectile dysfunction[d]	2 (10.5)	1 (5.3)
Oedema[b]	8 (22.2)	0 (0.0)
Fatigue[b]	11 (30.6)	0 (0.0)
Pyrexia	14 (38.9)	0 (0.0)
Laboratory Parameters[e]		
AST increased	18 (50.0)	1 (2.8)
ALT increased	21 (58.3)	3 (8.3)
Calcium decreased	22 (61.1)	4 (11.1)
Lymphocyte count decreased[e]	8 (27.6)	4 (13.8)
WBC count decreased[e]	15 (41.7)	2 (5.6)
Albumin decreased	19 (52.8)	0 (0.0)

Creatinine increased	7 (19.4)	1 (2.8)
Sodium decreased	6 (16.7)	0 (0.0)
Alkaline phosphatase increased	18 (50.0)	0 (0.0)
Platelets decreased[e]	10 (27.8)	1 (2.8)
Total bilirubin increased	11 (30.6)	1 (2.8)
Neutrophil count decreased[e]	14 (40.0)	3 (8.6)
Magnesium decreased	10 (27.8)	2 (5.6)
Haemoglobin decreased[e]	13 (36.1)	4 (11.1)
Potassium decreased	7 (19.4)	2 (5.6)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; FMQ = FDA Medical Query;tMedDRA = Medical Dictionary for Regulatory Activities; n = number of patients in the specified category;tN = number of patients; SMQ = standardized MedDRA query; WBC = white blood cell.ta As defined by FMQ.tb By composite terms (*italicized*).tc As defined by MedDRA SMQ.
d Erectile dysfunction in male patients treated with selpercatinib. Denominator adjusted because gender-specific
event for males (N = 19).
e Based on laboratory assessments. Percentage is calculated based on the number of patients with baseline assessment and at least 1 post-baseline assessment as the denominator, which was 29 for lymphocyte count decreased, 35 for neutrophil count decreased, and 36 for the others.

Laboratory findings

Clinical laboratory evaluations

Table 53. Treatment-Emergent Abnormal Haematologic Laboratory Tests (Safety Analysis Set)

		Overall Safety (N=36)					
		All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4
	n'	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
WBC Count Decreased	36	15 (41.7)	8 (22.2)	5 (13.9)	0 (0.0)	2 (5.6)	2 (5.6)
Neutrophil Count Decreased	35	14 (40.0)	2 (5.7)	9 (25.7)	2 (5.7)	1 (2.9)	3 (8.6)
Hemoglobin Increased	36	12 (33.3)	10 (27.8)	1 (2.8)	1 (2.8)	0 (0.0)	1 (2.8)
Hemoglobin Decreased	36	13 (36.1)	6 (16.7)	3 (8.3)	4 (11.1)	0 (0.0)	4 (11.1)
Platelets Decreased	36	10 (27.8)	8 (22.2)	1 (2.8)	1 (2.8)	0 (0.0)	1 (2.8)
Lymphocyte Count Increased	29	2 (6.9)	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte Count Decreased	29	8 (27.6)	3 (10.3)	1 (3.4)	1 (3.4)	3 (10.3)	4 (13.8)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; N = number of subjects in analysis group; n = number of subjects in
the specified category; WBC = White Blood Cell.
Percentage is calculated based on the number of patients with baseline assessment and at least one post-baseline assessment as the denominator (n').
The worst post-baseline toxicity grade is used for every subject.
Treatment-emergent post-baseline grade is a grade that is worse than baseline grade for a given parameter in either direction of increase or decrease.
Toxicity grade assignment based on CTCAE (v5.0): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening/ debilitating), Grade 5 (fatal).

Table 54. Treatment-Emergent Abnormal Chemistry Laboratory Tests (Safety Analysis Set)

		Overall Safety (N=36)									
		All Grades		Grade 1		Grade 2		Grade 3		Grade 4		Grade 3/4	
	n'	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Albumin Decreased	36	19	(52.8)	11	(30.6)	8	(22.2)	0	(0.0)	0	(0.0)	0	(0.0)
Alkaline Phosphatase Increased	36	18	(50.0)	16	(44.4)	2	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Alanine Aminotransferase Increased	36	21	(58.3)	17	(47.2)	1	(2.8)	3	(8.3)	0	(0.0)	3	(8.3)
Aspartate Aminotransferase Increased	36	18	(50.0)	15	(41.7)	2	(5.6)	1	(2.8)	0	(0.0)	1	(2.8)
Total Bilirubin Increased	36	11	(30.6)	5	(13.9)	5	(13.9)	1	(2.8)	0	(0.0)	1	(2.8)
Cholesterol Increased	18	5	(27.8)	5	(27.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Creatinine Increased	36	7	(19.4)	6	(16.7)	0	(0.0)	0	(0.0)	1	(2.8)	1	(2.8)
Calcium Increased	36	4	(11.1)	2	(5.6)	1	(2.8)	1	(2.8)	0	(0.0)	1	(2.8)
Calcium Decreased	36	22	(61.1)	11	(30.6)	7	(19.4)	2	(5.6)	2	(5.6)	4	(11.1)
Glucose Decreased	36	5	(13.9)	4	(11.1)	1	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Magnesium Increased	36	2	(5.6)	2	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Magnesium Decreased	36	10	(27.8)	8	(22.2)	0	(0.0)	0	(0.0)	2	(5.6)	2	(5.6)
Potassium Decreased	36	7	(19.4)	5	(13.9)	0	(0.0)	1	(2.8)	1	(2.8)	2	(5.6)
Potassium Increased	36	10	(27.8)	4	(11.1)	5	(13.9)	0	(0.0)	1	(2.8)	1	(2.8)
Sodium Increased	36	2	(5.6)	2	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Sodium Decreased	36	6	(16.7)	6	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; N = number of subjects in analysis group; n = number of subjects in
the specified category; WBC = White Blood Cell.
Percentage is calculated based on the number of patients with baseline assessment and at least one post-baseline assessment as the denominator (n').
The worst post-baseline toxicity grade is used for every subject.
Treatment-emergent post-baseline grade is a grade that is worse than baseline grade for a given parameter in either direction of increase or decrease.
Toxicity grade assignment based on CTCAE (v5.0): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening/ debilitating), Grade 5 (fatal).

Safety in special populations

Subgroup Analysis

No clinically meaningful differences in the safety profile across age groups were observed.

LIBRETTO-121 CSR provides safety data by age group in the **Overall Population** for the following:

- overview of AEs
- TEAEs by PT, adjusted for sex-specific AEs; by system organ class; and by composite terms
- Grade 3 or greater TEAEs by PT, system organ class, composite terms, and
- Grade 3 or greater TEAEs by PT, adjusted for sex-specific AEs.

The following safety data is provided by age group and tumour type (**MTC** or **PTC Population** only, due to small number of patients in age groups within the **Other Solid Tumours Population**):

- overview of AEs
- TEAEs by PT adjusted for sex-specific AEs, and
- Grade 3 or greater TEAEs by PT, adjusted for sex-specific AEs.

Safety related to drug-drug interactions and other interactions

Please refer to the PK section of this report.

Discontinuation due to adverse events

Treatment Discontinuations and Dose Modifications

TEAEs leading to dose interruption (withheld)

Table 55. Treatment-Emergent Adverse Events (TEAEs) Leading to Dose Interruption by Preferred Term and Tumour Type (Safety Analysis Set)

Preferred Term	Total (N=36) n (%)	MTC (N=15) n (%)	PTC (N=15) n (%)	Other (N=6) n (%)
Subjects with Any TEAEs Leading to Dose Interruption	15 (41.7)	7 (46.7)	7 (46.7)	1 (16.7)
Alanine aminotransferase increased	3 (8.3)	1 (6.7)	1 (6.7)	1 (16.7)
Aspartate aminotransferase increased	3 (8.3)	1 (6.7)	1 (6.7)	1 (16.7)
Ascites	2 (5.6)	0 (0.0)	2 (13.3)	0 (0.0)
Blood bilirubin increased	2 (5.6)	1 (6.7)	1 (6.7)	0 (0.0)
Neutrophil count decreased	2 (5.6)	0 (0.0)	2 (13.3)	0 (0.0)
Pyrexia	2 (5.6)	1 (6.7)	1 (6.7)	0 (0.0)
Abdominal pain	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Anaemia	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Blood creatine phosphokinase increased	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
Blood creatinine increased	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Blood lactate dehydrogenase increased	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)
Device related infection	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Diarrhoea	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Drug hypersensitivity	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Electrocardiogram QT prolonged	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Face oedema	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Gastrointestinal fistula	1 (2.8)	0 (0.0)	0 (0.0)	1 (16.7)
Lymphocyte count decreased	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Nasal congestion	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Nausea	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Oropharyngeal pain	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Pneumatosis intestinalis	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Pneumonia	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Upper limb fracture	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Vomiting	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Wound dehiscence	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)
Wound infection	1 (2.8)	1 (6.7)	0 (0.0)	0 (0.0)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis
group; n = number of subjects in the specified category; PTC = Papillary Thyroid Cancer; TEAE = Treatment-Emergent Adverse Event.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Treatment-emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of selpercatinib.
If a subject experienced more than one adverse event within a preferred term, the subject is counted once in that preferred term.
Reported adverse event terms were coded using MedDRA (version 21.1 or later).
TEAEs are sorted in decreasing order of frequency based on Overall Safety Analysis Set.

TEAEs leading to dose reduction

Table 56. Treatment-Emergent Adverse Events (TEAEs) Leading to Dose Reduction by Preferred Term and Tumour Type (Safety Analysis Set)

Preferred Term	Total (N=36) n (%)	MTC (N=15) n (%)	PTC (N=15) n (%)	Other (N=6) n (%)
Subjects with Any TEAEs Leading to Dose Reduction	8 (22.2)	3 (20.0)	4 (26.7)	1 (16.7)
Alanine aminotransferase increased	3 (8.3)	1 (6.7)	1 (6.7)	1 (16.7)
Neutrophil count decreased	2 (5.6)	0 (0.0)	2 (13.3)	0 (0.0)
Weight increased	2 (5.6)	2 (13.3)	0 (0.0)	0 (0.0)
Blood bilirubin increased	1 (2.8)	0 (0.0)	1 (6.7)	0 (0.0)

Data Exported 13-Dec-2024, Visit Cutoff 08-Nov-2024
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; MTC = Medullary Thyroid Cancer; N = number of subjects in analysis
group; n = number of subjects in the specified category; PTC = Papillary Thyroid Cancer; TEAE = Treatment-Emergent Adverse Event.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Treatment-emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of selpercatinib.
If a subject experienced more than one adverse event within a preferred term, the subject is counted once in that preferred term.
Reported adverse event terms were coded using MedDRA (version 21.1 or later).
TEAEs are sorted in decreasing order of frequency based on Overall Safety Analysis Set.

TEAEs leading to study drug discontinuation

One patient experienced a TEAE (pregnancy test positive) that led to permanent discontinuation of selpercatinib, which was considered as not related to the treatment by the investigator.

Table 57. Study Drug Dosage Modifications Due to Adverse Events by Age Group (Safety Analysis Set)

Status	Total (N=36) n (%)	2 to <6 years (N=3) n (%)	6 to <12 years (N=8) n (%)	12 to <18 years (N=20) n (%)	18 to <=21 years (N=5) n (%)
Any Dose Reduction Due to Adverse Event	6 (16.7)	0 (0.0)	2 (25.0)	4 (20.0)	0 (0.0)
ALANINE AMINOTRANSFERASE INCREASED	1 (2.8)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
ALT INCREASED	1 (2.8)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
BLOOD BILIRUBIN INCREASED	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
FACIAL EDEMA	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
NEUTROPHIL COUNT DECREASED	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
WOUND INFECTION	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Any Dose Interruption/Missed Due to Adverse Event	14 (38.9)	1 (33.3)	3 (37.5)	9 (45.0)	1 (20.0)
ALT INCREASED	2 (5.6)	0 (0.0)	1 (12.5)	1 (5.0)	0 (0.0)
BLOOD BILIRUBIN INCREASED	2 (5.6)	0 (0.0)	0 (0.0)	1 (5.0)	1 (20.0)
NEUTROPHIL COUNT DECREASED	2 (5.6)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
ABDOMINAL PAIN WORSENING	1 (2.8)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
ALANINE AMINOTRANSFERASE INCREASED	1 (2.8)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
ANEMIA	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
ASCITES	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
CHYLOUS ASCITES	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
CREATINE KINASE INCREASED	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
DRUG HYPERSENSITIVITY	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
ELBOW FRACTURE	1 (2.8)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
ELECTROCARDIOGRAM QTCORRECTED INTERVAL PROLONGED	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Any Dose Interruption/Missed Due to Adverse Event					
FACIAL EDEMA	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
GASTROINTESTINAL FISTULA	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
PNEUMINITIS INTESTINALIS	1 (2.8)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
RIGHT LOBAR PNEUMONIA	1 (2.8)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
WOUND INFECTION	1 (2.8)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)

Data Exported 10-Jan-2025, Visit Cutoff 08-Nov-2024
Abbreviations: N = number of subjects in analysis group; n = number of subjects in the specified category.
Percentage is calculated using the number of subjects in the column heading as the denominator.
A subject may be counted in multiple reasons but is only counted once in the overall status.
Reported adverse event terms were coded using MedDRA (version 21.1 or later).

Table 58. Study Drug Dosage Modifications by Tumour Type (Safety Analysis Set)

Status	Total (N=36)	MTC (N=15)	PTC (N=15)	Other (N=6)
Study Drug Modification Type and Reason (n, %)				
Any Dose Reduction	13 (36.1)	9 (60.0)	4 (26.7)	0 (0.0)
Adverse Event	6 (16.7)	3 (20.0)	3 (20.0)	0 (0.0)
Other Reasons	10 (27.8)	7 (46.7)	3 (20.0)	0 (0.0)
Any Dose Interruption/Missed	29 (80.6)	15 (100.0)	10 (66.7)	4 (66.7)
Adverse Event	14 (38.9)	7 (46.7)	6 (40.0)	1 (16.7)
Other Reasons	24 (66.7)	15 (100.0)	6 (40.0)	3 (50.0)
Drug Treatment Holiday	2 (5.6)	1 (6.7)	1 (6.7)	0 (0.0)
Duration of Drug Treatment Holiday (months)*a				
n	2	1	1	0
Mean	2.86	2.43	3.29	
Standard Deviation	0.604			
Median	2.86	2.43	3.29	
Minimum	2.4	2.4	3.3	
Maximum	3.3	2.4	3.3	

Data Exported 10-Jan-2025, Visit Cutoff 08-Nov-2024
Abbreviations: MTC = Medullary Thyroid Cancer; N = number of subjects in analysis group; n = number of subjects in the specified category;
PTC = Papillary Thyroid Cancer.
Percentage is calculated using the number of subjects in the column heading as the denominator.
A subject may be counted in multiple reasons but is only counted once in the overall status.
*a Duration of drug treatment holiday = (end date - start date + 1)/30.4375 for subjects who ended the drug treatment holiday prior to or on data cutoff date; duration of drug treatment holiday = (data cutoff date - start date + 1)/30.4375 for subjects continuing on drug treatment holiday as of data cutoff date.

Post marketing experience

Selpercatinib was first authorised on 08 May 2020 by FDA and has been granted marketing authorisation in 55 countries. Cumulatively, up to 31 October 2024, an estimated 9000 patients were exposed to selpercatinib worldwide. The data reported from the postmarketing setting were generally consistent with the known safety profile of selpercatinib. Most events were reported as nonserious, and the most frequently reported events were recognized ADRs for selpercatinib or clinically expected in the target indication.

Data for paediatric and adolescent patients exposed to selpercatinib in the postmarketing setting are very limited. A total of 20 cases (14 from individual/named patient use programmes, 4 spontaneous, and 2 from the literature). Of these 20 cases, 6 were reported in the age group of 2 years to less than 12 years. These 20 cases reported a total of 49 AEs (9 serious, 40 nonserious) to the MAH cumulatively as of 08 November 2024.

Overall, the data reported in paediatric and adolescent patients exposed to selpercatinib in the postmarketing setting are consistent with the known safety profile of selpercatinib or would not be unexpected in a population of patients with advanced cancer.

2.4.3.1. Discussion on clinical safety

Introduction

The data obtained in LIBRETTO-121 provided the primary basis of the use of selpercatinib in paediatric patients of 2 years of age and older with advanced solid tumours with RET alterations.

LIBRETTO-121 enrolled 36 pediatric or adolescent patients (median age: 13.0 years; range 2 to 20 years) with a sex ratio 1:1 which encompassed 15 *RET*-altered MTC, 15 *RET*-fusion PTC and 6 others solid tumours with *RET*-alterations. Paediatric patients from 2 years to less than 12 years of age represents 30.6% (n=11/36) of the overall population included in LIBRETTO-121 and are split in 5/15 MTC, 3/15 PTC and 3/6 with Other solid tumours.

Adverse events

All patients except one (n=35, 97.2%) present TEAE and among them 91.7% (n=33) were TEAE related to study drug by the investigator. More than half of patients presented TEAE Grade ≥3 (n=19, 52.8%). TE-SAEs were experienced by 19 patients (41.7%) including in 5 patients (13.9%) where TE-SAEs were considered related to study drug by the investigator.

Comparisons of TEAEs between defined age groups are not considered relevant due to the low numbers of events/ patients included by group (2 to <6 years (n=3), 6 to < 12 years (n=8), 12 to < 18 years (n=20) and 18 to < 21 years (n=5)).

The most commonly reported TEAEs of any grade were diarrhoea (n=17, 47.2%), nausea (n=15, 41.7%), and aspartate aminotransferase (AST) increased (n=14, 38.9%). These TEAE were already mentioned in the SmPC as very common (≥ 1/10) ADR in patients receiving selpercatinib in previous adolescent and adult population studied (n=1188).

More than a half had grade 3 or higher TEAEs in overall population (n=19, 52.8%) (occurring in at least 2 patients): weight increased (n=4, 11.1%), alanine aminotransferase (ALT) increased (n=3, 8.3%), vomiting (n=3, 8.3%), anaemia (n=2, 5.6%), constipation (n=2, 5.6%), hypertension (n=2, 5.6%), hypokalemia (n=2, 5.6%), and neutrophil count decreased (n=2, 5.6%).

Safety results of the overall paediatric population (n=36) were broadly consistent with those observed in adult trials, although some differences were noted:

- **Epiphysiolysis of the femoral head** (n=1, 2.8%) had been identified as an adverse drug reaction in the adolescent population. No new AEs related to early growth plate closure were identified in this analysis.
- **Musculoskeletal pain** (n=21, 58.3%) as composite terms was the most frequent TEAE observed in paediatric population.
- **Weight increased** (n=3, 8.3%) was observed as part of drug-related grade≥3.
- **Foetal death** (n=1, 2.8%) was reported as part of drug-related grade 4 TE-SAE.
- Absence of **interstitial lung disease/pneumonitis** (both n=0) reported in the Overall Population contrary to previous studies in adult population.
- Dental evaluation was monitored due to preclinical safety data and no AEs reported were related to study drug by the investigator.
- Pubertal maturation was also closely assessed, and no delay appeared in paediatric population.

Following the skeletal findings in non-clinical studies, the MAH submitted as part of a separate application (Retsevmo II-30), a review on events of slipped capital femoral epiphysis (SCFE) or slipped upper femoral epiphysis (SUFE) reported in paediatric patients with selpercatinib and updated sections 4.4 and 4.8 of the SmPC in order to add a new warning on 'Epiphysiolysis of the femoral head in Paediatric Patients' and to add it to the list of adverse drug reactions (ADRs) with frequency 'Common'. No further PI updates are warranted based on the currently available data.

Serious adverse events / Deaths

No patients discontinued the study treatment due to TE-SAEs.

Four deaths occurred during the study in patients with Other Solid Tumours, and all were attributed to disease progression.

AESIs

The AESIs AST increased, ALT increased, Hypertension, Hypersensitivity, and ECG QT prolongation are recognised as ADRs for selpercatinib and are listed in the SmPC. The AESIs are monitorable and manageable with successful dose modification strategies, which allow most patients who experience these events to continue therapy. See paragraph on 'Management of toxicities: Treatment Discontinuations and Dose Modifications' below.

An evaluation of AESIs from LIBRETTO-121 did not identify any significant new information; most of the AESIs in this study were low grade (Grade 1 or Grade 2) and manageable with dose interruptions or reductions. None of the AESIs led to permanent discontinuation. Overall, AESIs were generally consistent with the known safety profile of selpercatinib, and no clinically significant differences were observed between the MTC, PTC, and Other Solid Tumours Populations when compared with the Overall Population.

Other Significant AEs

An evaluation of the following AEs, which have a warning or precaution associated in the current SmPC for Retsevmo, did not identify any clinically significant differences compared with the Overall Population: Haemorrhages (SMQ), Hypothyroidism (SMQ), Impaired wound healing and Embryo-foetal toxicity.

Other Safety Evaluations

No significant changes were observed in growth plate evaluation in patients who had not reached full adult height, in tooth development in patients aged at least 5 years without their full set of permanent teeth, or delay in sexual maturity in patients aged at least 7 years who had not reached

Tanner V at study enrolment. QTcF increase was already known in adolescent and adult patients treated with selpercatinib. SmPC was updated to align the QTcF interval prolongation for patients under 12 years old before starting selpercatinib treatment with the exclusion criteria of LIBRETTO-121 and medical understanding (Antoniou et al. 2017) to include patients that should have a QTcF interval of ≤440 ms.

Adverse Drug Reactions

As of the data cut-off of 08 November 2024, no new ADRs specific to the paediatric population have been identified. Also, no new information on the previously recognised ADR of epiphysiolysis (EMEA/H/C/005375/II/0030) was identified.

For the newly added ADR of erectile dysfunction in the MTC male adult population on selpercatinib therapy (EMEA/H/C/005375/R/0035), no clinically significant data was identified for the paediatric population that would support its relevance in the paediatric population.

In general, there were no clinically significant differences noted in the safety profile of selpercatinib between the data in the initial submission (data cut-off 13 January 2023) and this Clinical Overview regarding ADRs as of the latest 08 November 2024 data cut-off.

Therefore, in Section 4.8 of the SmPC, the statement that apart from epiphysiolysis of the femoral head, no other unique safety findings in children less than 18 years have been identified remains accurate. No further updates to Section 4.8 are proposed except to reflect the latest number of paediatric patients enrolled in LIBRETTO-121 by age and tumour type.

Of note, interstitial lung disease/pneumonitis were not observed in paediatric population as ADRs contrary to the adult population treated with selpercatinib.

Laboratory findings

The worsening of the postbaseline values for TE haematology and chemistry was generally infrequent and not considered clinically meaningful for the Overall Population.

Management of toxicities: Treatment Discontinuations and Dose Modifications.

No permanent discontinuations due to TEAEs except pregnancy (n=1) were reported, demonstrating tolerability. The follow-up of patient's toxicities seems acceptable in accordance with recommended dose modifications of the SmPC, which allow almost patients who experience these events to continue therapy without grade 4 or fatal grade TEAE:

Table 59. Recommended dose modifications for Retsevmo for adverse reactions based on body weight and BSA

Dose modification	Paediatric 2 to <12 years of age with BSA ≥1.53 m^2	Paediatric 2 to <12 years of age with BSA 1.09 to 1.52 m^2	Paediatric 2 to <12 years of age with BSA 0.66 to 1.08 m^2	Paediatric 2 to <12 years of age with BSA 0.45 to 0.65 m^2
Starting dose	160 mg orally twice daily	120 mg orally twice daily	80 mg orally twice daily	40 mg orally three times daily
First dose reduction	120 mg orally twice daily	80 mg orally twice daily	40 mg orally twice daily	40 mg orally twice daily
Second dose reduction	80 mg orally twice daily	40 mg orally twice daily	40 mg orally once daily	40 mg orally once daily
Third dose reduction*	40 mg orally twice daily	40 mg orally once daily	Permanently discontinue	Permanently discontinue

*Permanently discontinue selpercatinib in patients unable to tolerate three dose reductions

Additional considerations

In the context of the Conditional Marketing Authorisation (CMA) for Retsevmo, with the current application the following specific obligation (SOB) is considered fulfilled, and therefore it is recommended that it is deleted from the Annex II: *In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive thyroid cancer, the MAH should submit the final data from the study LIBRETTO-121 (Due date: 30 June 2025).*

2.4.3.2. Conclusions on clinical safety

In conclusion, selpercatinib continues to be tolerated in paediatric patients, with key toxicities that are generally consistent with the known safety profile of selpercatinib and overall manageable with few discontinuations due to AEs.

2.5. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 17.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 17.1 with the following content:

Safety concerns

Table 60. Summary of safety concerns

Summary of Safety Concerns	
Important identified risk(s)	-

Important potential risk(s)	Liver injury Cardiac arrhythmia due to QT prolongation Reproductive and developmental toxicities Growth plate abnormalities in paediatric patients
Missing information	Exposure and safety in patients with severe hepatic impairment Exposure and safety in patients with cardiac impairment

Pharmacovigilance plan

No additional pharmacovigilance activities.

Risk minimisation measures

Table 61. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Liver injury	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Cardiac arrhythmia due to QT prolongation	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Reproductive and developmental toxicity	**Routine risk minimisation measures:** SmPC Section 4.6 **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Pregnancy Data Collection – Maternal and Paternal • Pregnancy Outcome – Maternal and Paternal **Additional pharmacovigilance activities:** Study: None
Growth plate abnormalities in paediatric patients	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.3 **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Exposure and safety in patients with severe hepatic impairment	**Routine risk minimisation measures:** A clinical pharmacology study assessing the effect of hepatic impairment on the pharmacokinetics of selpercatinib is completed. SmPC is updated based on the safety and pharmacokinetic data. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Exposure and safety in patients with cardiac impairment	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None

Abbreviation: SmPC = Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2, of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The Retsevmo package leaflet met the pass criteria for readability testing. The Retsevmo package leaflet is now being modified to include paediatric patients 2 years and older with RET mutant MTC, RET fusion positive thyroid cancer and RET fusion positive solid tumours. In addition, the package leaflet is modified to include dosing and alternative administration instructions (dispersal of the approved tablet formulation) to support dosing these younger paediatric patients. The proposed text modifications to the package leaflet resulting from these changes do not have a significant impact on the design and readability and do not include text that is significantly different from that already user tested. Overall, the structure and design of the revised Retsevmo package leaflet have not changed due to the new information and the revisions do not significantly affect the overall readability.

2.7.2. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Retsevmo (selpercatinib) is removed from the additional monitoring list as

- it was approved more than five years ago and
- the conditions to the marketing authorisation (specific obligations) have been fulfilled.

Therefore the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH is seeking an extension of the indications for selpercatinib to patients aged 2 years and older.

The agreed wording of indication is the following:

Retsevmo as monotherapy is indicated for the treatment of adults and ***paediatric patients 2 years of age*** *and older with:*

- *advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate). For biomarker-based patient selection, see section 4.2.*
- *advanced RET-mutant medullary thyroid cancer (MTC). For biomarker-based patient selection, see section 4.2.*
- *advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted. For biomarker-based patient selection, see section 4.2.*

The proposed recommended dosing regimen for paediatric and adolescent patients aged from 2 to 18 years is as follows:

- BSA-based dosing (92 mg/m^2, rounded by 40-mg intervals based on capsule/tablet strengths) for paediatric patients 2 to less than 12 years of age
- Weight-based dosing (120 mg BID less than 50 kg and 160 mg BID 50 kg and over) for adolescent patients 12 years and older

3.1.2. Available therapies and unmet medical need

At present, for patients aged 12 or over with advanced *RET*-activated thyroid cancer (MTC or PTC), selpercatinib as monotherapy is already authorised (i.e. first and second line). No systemic agents are approved specifically for younger patients (aged 2 to 11) with advanced *RET*-fusion thyroid cancer, as well as for patients (aged 2 to under 18) with *RET*-activated solid tumours (regardless of histology).

Regarding children aged 5 years and older, vandetanib is approved for the treatment of unresectable locally advanced or metastatic mutant medullary thyroid cancer (MTC).

3.1.3. Main clinical studies

The MAH presented efficacy and safety analyses to support extension of the indications for selpercatinib to patients aged 2 years and older, including selected paediatric patients enrolled and treated in LIBRETTO-121. LIBRETTO-121, the paediatric study in the selpercatinib programme, is a phase I/II single arm study including a paediatric dose escalation and dose expansion cohorts. This study included 36 patients aged 2 to ≤20 years. Of the 36 patients, 14 patients had RET-mutant MTC, 1 patient had RET-fusion positive MTC, 15 patients had RET-fusion positive thyroid cancer, 3 patients had RET fusion-positive other solid tumours, and 3 patients had RET-mutant other solid tumours.

To support effectiveness, the final data analysis was provided with a cut-off date of November 8, 2024.

3.2. Favourable effects

PK data from paediatric patients in studies JZJU and JZJJ, together with the PPK model simulations, supported the use of the already approved formulations for Retsevmo in the paediatric population applied in this application (from 2 years of age). Posology recommendations based on BSA have been included in section 4.2 of the SmPC.

- *Overall population*

In the 36 patients, selpercatinib showed a BICR-confirmed overall response rate (ORR) of 52.8% (19 confirmed responses) (95% CI: 35.5, 69.6), with 10/19 patients with complete response (CR). In the population targeted by this extension of indication (2 to 11 years), an objective response was observed in 7 of the 11 patients (63.6%) in this age group.

In the 36 patients, responses appeared durable, with median DOR NE (95% CI: 33.4, NE) after a median follow-up of 35.06 months (interquartile range: 18.2, 44.2). 84.2% of patients were in response at least 12 months.

- *RET- mutant MTC*

In the 14 patients, selpercatinib showed a BICR-confirmed overall response rate (ORR) of 57.1%, (8 confirmed responses) (95% CI: 28.9, 82.3), with 5/8 patients with complete response (CR). In the population targeted by this extension of indication (2 to 11 years), an objective response was observed in all patients (n=5, 100%) with RET-mutant MTC, in this age group.

In the 14 patients, responses appeared durable, with median BICR-assessed confirmed DOR for responders not reached (95% CI: 24.9, NE) after a median follow-up of 44.19 months.

- *RET Fusion−Positive PTC*

In the 15 patients, selpercatinib showed a BICR-confirmed overall response rate (ORR) of 53.3%, (8 confirmed responses) (95% CI: 29.6, 78.7), with 4/8 patients with complete response (CR).

Responses appeared durable, with median BICR-assessed confirmed DOR for responders not reached (95% CI: NE, NE) after a median follow-up of 36.57 months.

- *Other Solid Tumours*

In the 6 patients, selpercatinib showed a BICR-confirmed overall response rate (ORR) of 33.3% (95%CI 4.3, 77.7). (2/6) patients responded to selpercatinib treatment, both with PR.

3.3. Uncertainties and limitations about favourable effects

The efficacy dataset of LIBRETTO-121 is very limited (36 patients in total: 14 patients had RET-mutant MTC, 1 patient had RET-fusion positive MTC, 15 with RET-fusion PTC, and 6 with other tumour types). Only 11 patients (30%) were aged 2 to <12 years, including 5 with RET-mutant MTC, 3 with RET-fusion PTC, and 3 with other tumours.

The small sample size and single-arm design make the study exploratory, and PFS and OS are difficult to interpret under these conditions. Nevertheless, given the rarity of the disease—particularly in the paediatric population—these limitations had been anticipated.

3.4. Unfavourable effects

All patients except one (n=35, 97.2%) present TEAE and among them 91.7% (n=33) were TEAE related to study drug by the investigator. More than half of patients presented TEAE Grade ≥3 (n=19, 52.8%). TE-SAEs were experienced by 19 patients (41.7%) including in 5 patients (13.9%) where TE-SAEs were considered related to study drug by the investigator.

The safety results of the overall population (n=36) were almost consistent with adult trial results but differences were highlighted concerning the following points:

- Epiphysiolysis of the femoral head (n=1, 2.8%) had been identified as an adverse drug reaction in the adolescent population. No new AEs related to early growth plate closure were identified in this analysis.
- Musculoskeletal pain (n=21, 58.3%) as composite terms was the most frequent TEAE observed in paediatric population.
- Weight increased (n=3, 8.3%) was observed as part of drug-related grade≥3.
- Foetal death (n=1, 2.8%) was reported as part of drug-related grade 4 TE-SAE.
- Absence of interstitial lung disease/pneumonitis (both n=0) reported in the Overall Population contrary to previous studies in adult population.
- Dental evaluation was monitored due to preclinical safety data and no AEs reported were related to study drug by the investigator.
- Pubertal maturation was also closely assessed and no delay appeared in paediatric population.

A total of 15 patients (41.7%) experienced TEAEs that led to selpercatinib being interrupted, 8 patients (22.2%) experienced TEAEs that led to a dose reduction, and 1 patient experienced a TEAE (pregnancy test positive) that led to permanent discontinuation of selpercatinib.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Effects Table

Table 62. Effects Table for Selpercatinib for the Treatment of Paediatric Patients 2 years of age and older with Advanced Solid Tumours with *RET* Alterations (data cut-off: 08 November 2024)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects in the Paediatric Patients with Advanced Solid Tumours with *RET* Alterations (n=36)						
ORR	Rate	n (%) (95% CI)	*19 (52.8)* *(35.5, 69.6)*	NA	- Absence of comparative data - Limited number of patients included - Immature data	Efficacy section of AR
DoR	Median	Months (95% CI)	NE (33.4, NE)	NA		
Unfavourable Effects in overall paediatric population (n= 36)						
AEs grade ≥3	related to study drug by the investigator	n (%)	13 (36.1%)	NA		
SAEs	related to study drug by the investigator	n (%)	5 (13.9%)	NA		
QT prolongation	AE of special interest	n (%)	5 (13.9%) Grade ≥ 3: 1 (2.8%)	NA		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
AST increased	AE of special interest	n (%)	14 (38.9%) Grade ≥ 3: 1 (2.8%)	NA		
ALT increased	AE of special interest	n (%)	12 (33.3%) Grade ≥ 3: 3 (8.3%)	NA		
Hypertension	AE of special interest	n (%)	3 (8.3%) Grade ≥ 3: 2 (5.6%)	NA		
Hypersensitivity	AE of special interest	n (%)	4 (11.1%) Grade ≥ 3: (n=1, 2.8%)	NA		

Abbreviations: CSR=Clinical study report, HR=Hazard ratio, NA=not applicable, ORR=Objective response rate, OS=Overall survival, PFS=Progression-free survival, DOR= duration of response

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Regarding the extension of indication for selpercatinib as monotherapy to paediatric patients aged 2 to 11 years with thyroid cancer with RET alterations, the efficacy results (ORR and DoR) indicate that the observed tumour reduction can be attributed to selpercatinib.

Due to the single-arm design of the pivotal study LIBRETTO-121, time to event endpoints such as progression-free survival (PFS), and overall survival (OS) cannot be interpreted.

Hereditary MTC is characterised by germline mutations in the RET proto-oncogene. As the underlying genetic mechanism is identical in paediatric and adult patients, similar efficacy of selpercatinib across age group can be expected. Although the number of paediatric patients was low, the observed response rate is considered promising, albeit lower than those reported in adults. Differences between paediatric and adult results were analysed, and potential contributors to the lower paediatric response rate were identified, including a higher number of lines of pretreatment, and inclusion of paediatric patients with non-measurable disease, in whom response is difficult to detect.

For the extension of indication for selpercatinib as monotherapy for the paediatric patients 2 years and older with advanced RET fusion-positive solid tumours, no direct comparison of the pathophysiology of these tumours in children and adults is possible. However, constitutive RET activation is the common pathogenic mechanism, independent of age. The safety profile of the overall population (n=36) was generally consistent with adult trial results, with some differences noted. The safety profile of paediatric and adolescent patients treated with selpercatinib based on LIBRETTO-121 is described in the SmPC.

3.7.2. Balance of benefits and risks

The B/R for selpercatinib in the sought indications, is positive.

3.8. Conclusions

The overall B/R of Retsevmo is positive in the sought indications.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I, II, and IIIB

Extension of indication to include paediatric patients 2 years and older with: (1) Advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory, (2) Advanced RET-mutant medullary thyroid cancer, (3) Advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted, for RETSEVMO, based on final results from study J2G-OX-JZJJ (LOXO RET 18036, LIBRETTO-121) listed as a specific obligation in Annex II; this is a multicentre, open-label Phase 1/2 study in paediatric patients with advanced solid or primary CNS tumours harbouring an activating RET alteration. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. Annex II is updated to reflect the completion of the Specific Obligation and the CHMP recommendation to grant a marketing authorisation no longer subject to specific obligation. The Package Leaflet has been updated in accordance. Version 17.1 of the RMP has also been submitted.

The variation leads to amendments to the annex(es) I, II, and IIIB and to the Risk Management Plan (RMP).

As a result of this variation, the SmPC, Annex II and PL are also updated to reflect the completion of the specific obligation and the CHMP recommendation to grant a marketing authorisation no longer subject to specific obligations.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

The following obligation has been fulfilled, and therefore it is recommended that it is deleted from the Annex II to the opinion and that the marketing authorisation is granted not subject to specific obligations:

Description	Due date
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive thyroid cancer, the MAH should submit the final data from the study LIBRETTO-121.	30 June 2025

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0133/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Retsevmo is not similar to Lutathera, Onivyde pegylated liposomal, Zejula, Pemazyre, Kimmtrak, Xermelo, Qarziba, Ayvakyt, Koselugo, SomaKit TOC, Qinlock, Crysvita, Vyloy, Finlee, Elahere, Tibsovo, Hetronifly, Spexotras, Zynyz, Ogsiveo, Ziihera, Ojemda and Voranigo. within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.