25 January 2023
EMA/60663/2024
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Retsevmo

International non-proprietary name: selpercatinib

Procedure No. EMEA/H/C/005375/II/0021

Note

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

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anaplastic thyroid cancer
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours
BID	twice daily
CBR	clinical benefit rate
CSR	clinical study report
CI	confidence interval
C_{max}	maximum drug concentration
CR	complete response
DTC	differentiated thyroid cancer
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EU	European Union
FTC	follicular thyroid cancer
IRC	Independent Review Committee
MKI	multikinase inhibitor
MTC	medullary thyroid cancer
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBT	PBT (persistent and bioaccumulative and toxic)
PD	progressive disease
PDTC	poorly differentiated thyroid carcinoma
PFS	progression-free survival

PK	Pharmacokinetic(s)
PR	partial response
PT	preferred term
PTC	papillary thyroid cancer
QD	Once daily
RAI	radioactive iodine
RECIST	Response Evaluation Criteria in Solid Tumors
RET	REarranged during Transfection
SAE	serious adverse event
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event)
TC	thyroid cancer
TC:TrtSys	Patients Previously Treated with systemic therapy
TC:TrtSysNaïve	Patients Not Previously Treated with systemic therapy other than RAI
TESAE	treatment-emergent SAE
vPBT	Very PBT (persistent and bioaccumulative and toxic)

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 30 November 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer in the first-line setting for RETSEVMO based on interim data from studies LIBRETTO-001 (LOXO-RET-17001) and LIBRETTO-121; LIBRETTO-001 is an open-label, multicentre, global Phase 1/2 study of selpercatinib in patients with RET-altered advanced solid tumors. LIBRETTO-121 is a Phase 1/2 study of selpercatinib in paediatric patients with advanced RET-altered solid or primary central nervous system tumours. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.2 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision PIP decision number: P/0133/2023 on the agreement of a paediatric investigation plan (PIP).

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.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

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	30 November 2022
Start of procedure:	31 December 2022
CHMP Rapporteur Assessment Report	28 February 2023
PRAC Rapporteur Assessment Report	2 March 2023
PRAC members comments	8 March 2023
PRAC Outcome	16 March 2023
CHMP members comments	20 March 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 March 2023
Request for supplementary information (RSI)	30 March 2023
CHMP Rapporteur Assessment Report	26 June 2023
PRAC Rapporteur Assessment Report	27 June 2023
PRAC Outcome	6 July 2023
CHMP members comments	10 July 2023
Updated CHMP Rapporteur Assessment Report	17 July 2023
Request for supplementary information (RSI)	20 July 2023
CHMP Rapporteur Assessment Report	11 October 2023
PRAC Rapporteur Assessment Report	16 October 2023
PRAC Outcome	26 October 2023
CHMP members comments	27 October 2023
Updated CHMP Rapporteur Assessment Report	31 October 2023
Request for supplementary information (RSI)	9 November 2023
CHMP Rapporteur Assessment Report	20 December 2023
CHMP members comments	15 January 2024
Updated CHMP Rapporteur Assessment Report	19 January 2024
Opinion	25 January 2024

2. Scientific discussion

2.1.1. Problem statement

Disease or condition

The MAH is seeking an extension of indication for selpercatinib as monotherapy for adults with advanced *RET* fusion-positive thyroid cancer without prior standard first line therapy (i.e. first-line setting).

Additionally, the MAH is seeking an extension of indication for selpercatinib as monotherapy for adolescents (≥ 12 years of age) with advanced *RET* fusion-positive thyroid cancer (i.e. first and later line).

Epidemiology

The thyroid follicle-derived, differentiated cancers (papillary thyroid cancer [PTC] and follicular thyroid cancer [FTC]) are the most common thyroid cancers, accounting for 80% to 85% and 10% to 15% of all thyroid cancer cases, respectively (Aboelnaga and Ahmed 2015). Poorly differentiated subtypes [PDTC] and anaplastic thyroid cancer [ATC]) account for 5% to 10% of thyroid cancers and are characterized by less differentiated histologic features and more aggressive clinical behaviour than the differentiated subtypes (Landa 2016).

RET gene fusions have been identified in approximately 6% to 9% of PTCs and approximately 6% of PDTCs (Fusco 1987; Agrawal 2013; Cancer Genome Atlas Research 2014; Kato 2017; Landa 2016). In contrast to PTC and PDTC, neither FTC nor ATC are frequently associated with RET gene fusions. Most differentiated thyroid cancers, including PTC, are largely asymptomatic, treatable tumours with an excellent prognosis after surgical resection and radioiodine therapy (Pacini et al., 2012).

In Europe, an estimated 53,000 patients developed thyroid cancer in 2012. Assuming 84% of those cases were PTC (44,520), and assuming RET- fusion gene alterations, according to more recent data (Santoro 2020), are present in 11% of PTC patients the incidence of new cases of RET- fusion positive PTC was approximately 4900 per year (ENRC 2019; Roskoski and Sadeghi-Nejad 2018).

Although extremely rare, the most common form of thyroid cancer in children is PTC. In addition, children with differentiated thyroid cancer have a higher prevalence of gene rearrangements (Segni et al. 2017). Thyroid carcinomas occurring in children carry a unique set of clinical, pathologic, and molecular characteristics.

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, diagnosis and stage/prognosis

The clinical course of RET fusion-positive PTC is heterogeneous, varying from some tumours being cured by surgical resection to aggressive cancers associated with metastases and high mortality. Recurrent disease is treated with reoperation and/or radioactive iodine therapy. However, these treatments are associated with significant morbidity and are often not curative.

In comparison to adults, children more often present with aggressive, advanced stage disease. This is at least in part due to the underlying biologic and molecular differences between paediatric and adult thyroid cancer. Specifically, papillary thyroid carcinoma (which accounts for approximately 90% of paediatric

thyroid cancer) has a high rate of gene fusions (50-60%, compared to approximately 15% seen in adults) and are associated with more extensive extrathyroidal disease (Starenki and Park 2015).

The prognosis is favourable for the papillary and follicular subtypes of thyroid cancer, as they are slower-growing, indolent and rarely fatal cancers, as evidenced by the high 5-year relative survival in the EUROCARE-5 study (greater than 95% in PTC and 87% in follicular thyroid cancer (Dal Maso et al. 2017). In the US, the 5-year survival rate for metastatic PTC is 78% compared to 99% for localised cancer (ASCO 2019).

Management

Patients with *RET* fusion-positive PTC or PDTC receive standard of care for their thyroid cancer subtype. Standard treatment options for PTC, include surgery and radioactive iodine (RAI) (Nguyen et al. 2015). PDTC is less responsive to radioactive iodine than PTC. Paediatric patients with PTC are also treated with surgical resection and RAI therapy, although the specifics of RAI are somewhat different in this population (Paulson et al. 2019).

No systemic agents are approved specifically for patients with advanced *RET*-fusion thyroid cancer.

Two available multikinase inhibitors (MKIs), sorafenib and lenvatinib, are approved for the treatment of unresectable, iodine-refractory differentiated thyroid cancer, irrespective of the presence or absence of a *RET* mutation.

2.1.2. About the product

Selpercatinib is an inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase (including KIF5B-RET and CCDC6-RET).

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

As of today the approved indications are 1) the treatment of advanced RET fusion-positive NSCLC in adult patients not previously treated with a RET inhibitor, 2) advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib and 3) advanced RET-mutant MTC in adult and pediatric patients 12 years of age and older.

The conditional MA was approved based on ORR and DOR observed in the ongoing Phase 1/2 study, LIBRETTO-001.

The presence of a RET gene fusion or mutation should be confirmed by a validated test prior to initiation of treatment with Retsevmo.

The recommended dose of Retsevmo based on body weight is:

-Less than 50 kg: 120 mg twice daily.

-50 kg or greater: 160 mg twice daily.

If a patient vomits or misses a dose, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken.

Treatment should be continued until disease progression or unacceptable toxicity.

The applied indication is:

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with:

– advanced *RET* fusion-positive thyroid cancer

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

Evaluation of clinical safety and efficacy of selpercatinib in patients with RET fusion-positive tissue is based on the analysis of interim data from LIBRETTO-001 (LOXORET- 17001; J2G-OX-JZJA) and LIBRETTO-121 Study. LIBRETTO-001 is a global, multicohort, open-label, phase 1/2 study in adult and adolescent with advanced RET-altered tumours. LIBRETTO-121 is a multicentre, open-label, Phase 1/2 study in paediatric patients with an advanced solid or primary central nervous system tumour harbouring, an activating RET alteration.

Table 1. Regulatory interactions in the EU for Retsevmo

Date	Regulatory Interaction
08 November 2019	PIP Decision: Condition: Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms). A waiver was granted • which applies to the paediatric population from birth to less than 6 months of age • which applies to capsule, hard, age-appropriate dosage form, oral use, and • on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible
	Indications: Treatment of adolescents with *RET*-mutant MTC who require systemic therapy, have progressed following prior treatment, and have no acceptable alternative treatment options. Treatment of paediatric patients with *RET*-altered, locally advanced or metastatic, solid tumours or primary CNS tumours
11 February 2021	EC 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
21 June 2022	Approval of extension of indication to include first-line treatment of adults with advanced *RET* fusion-positive NSCLC not previously treated with a RET inhibitor
02 September 2022	Approval of extension of indication to include first-line treatment of adults and adolescents 12 years and older with advanced *RET*-mutant MTC

Abbreviations: CNS = central nervous system; EC = European Commission; MA = marketing authorisation; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; PIP = paediatric investigation plan; *RET* = REarranged during Transfection; TC= thyroid cancer.

The 13 April 2023, a decision on the acceptance of a modification of an agreed PIP for selpercatinib has been issued.

2.1.4. General comments on compliance with GCP

The Applicant stated that clinical trials that support this use of selpercatinib were conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS)

International Ethical Guidelines for Biomedical Research Involving Human Subjects,

2) the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guideline (E6), and

3) applicable laws and regulations of the country or countries where a study is conducted.

The Applicant also stated that clinical trials conducted outside the European Union meet the ethical requirements of Directive 2001/20/EC4 GCP.

Table 2. Clinical studies contained in this application that were inspected by regulatory authorities

Name	Agency Name(s)	Begin Date	End Date	Observations?
University of Texas MD Anderson Cancer Center - Subbiah	US FDA	08-Jan-2020	14-Jan-2020	No
The Ohio State University - Shah	US FDA	27-Jan-2020	07-Feb-2020	Yes (1 Not Classified observation)
Massachusetts General Hospital - Wirth	US FDA	30-Jan-2020	10-Feb-2020	No
Japan Affiliate	Pharmaceuticals and Medical Devices Agency of Japan (PMDA)	17-May-2021	17-May-2021	No
Medpace Singapore Pte Ltd	Health Sciences Authority (Singapore Regulatory Agency)	12-Jul-2021	14-Jul-2021	Yes (2 Major, 3 Minor/Other Observations)
Korea Affiliate	Korea Ministry of Food and Drug Safety (MFDS)	02-Sep-2021	03-Sep-2021	Yes (1 Minor/Other Observation)

Abbreviation: N/A = not applicable; US FDA = United States Food and Drug Administration.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

Prevalence of Currently Authorised Indications

Selpercatinib is currently authorised for patients with thyroid cancer (medullary, papillary, and other subtypes) and lung cancer (NSCLC subtype), specifically those that have activated RET through alterations of the RET gene such as fusions and mutations. Patients tested for gene alterations and only those positive can be dosed with selpercatinib.

The prevalence of the indications for selpercatinib was derived from the prevalence of each cancer type in each EU member state using 3-year prevalence data (IARC, accessed 2022) and then refined for the frequency of the indicated cancer subtypes and the frequency of activated RET in that subtype. The 3-year prevalence data was used instead of 1-year data because some patients may have been treated with selpercatinib longer than one year. Cancer prevalence was not adjusted for cancer stage or whether patients have received prior treatment with other cancer medicine or for use in only adults with the cancer, these assumptions will also result in conservatism in the PEC calculations.

Since the PECsurface water was greater than 0.01 µg·L-1, a Phase II risk assessment has been conducted. Summary of the main study results are presented below.

Table 3. Summary of main study results

Substance (INN/Invented Name): Selpercatinib / Retsevmo			
CAS-number : 152628-33-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 …	log Kow = 1.30 at pH 5 log kow = 3.08 at pH 7 log kow = 3.45 at pH 9	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log Kow	pH 5 = 1.30 pH 7 = 3.08 pH 9 = 3.45	not B
	BCF (steady-state lipid-normalised) (OECD 305)	336 (low concentration) and 130 (high concentration)	
Persistence	DT50 or ready biodegradability	Sediment (two systems): - DT_{50} water: 10, 9.8 d - DT_{50} sediment: 353, 348 d - DT_{50} whole system: 269, 338 d	vP
Toxicity	NOEC *Daphnia* sp. Reproduction Test (OECD 211)	NOEC = 97 µg/L Toxicity to reproduction observed	T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.033	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical			(N)

class)					
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	*Soil*: K_{OC} = 116050 L/kg (soil 1) K_{OC} = 341959 L/kg (soil 2) K_{OC} = 582830 L/kg (soil 3) K_{OC} = 240301 L/kg (soil 4) *Sludge:* K_{OC} = 683 L/kg (sludge 1) K_{OC} = 1180 L/kg (sludge 2) K_{OC} = 1102 L/kg (sludge 3)			Average K_{OC} soil = 320285 L/kg
Ready Biodegradability Test	OECD 301				NA
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	System 1 at 12°C - DT_{50}, water = 10 d - DT_{50}, sediment = 353 d - DT_{50}, whole system = 269 d - shifting to sediment = 97.6% System 2 at 12°C - DT_{50}, water = 9.8 d - DT_{50}, sediment = 348 d - DT_{50}, whole system = 338 d - shifting to sediment = 99.4%			Two water, sediment systems evaluated. Sediment risk assessment triggered. Very persistent in sediments
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	1700	µg/L	*Raphidocelis subcapitata* Growth rate Yield
Daphnia sp. Reproduction Test	OECD 211	NOEC	97	µg/L	*Daphnia magna* Production of immobile offspring
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	160	µg/L	*Pimephales promelas* Total length, wet weight, dry weight
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	>1000000	µg/L	Total respiration
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF BCF_{KgL}	11 (low concentration) and 9.0 (high concentration) 98 (low concentration) and 42 (high concentration)	L/kg	%lipids: 50% at 126 d 50% at 61 d
Sediment dwelling organism	OECD 218	NOEC	1987	mg/kg	*Chironomus riparius* Female and male

					development rate; concentration as dry weight, normalized to 10% organic carbon.

2.2.2. Discussion and conclusion on non-clinical aspects

No new non-clinical data, have been submitted in this application, which is considered acceptable.

An updated ERA was submitted with this extension of indication.

All initial data from Phase I and II trials, which had already been considered compliant, are used to calculate the new PEC/PNEC ratios.

Selpercatinib does not appear to present a risk for aquatic organisms in the environment and is not classified as PBT or vPvB.

2.3. Clinical aspects

2.3.1. Introduction

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.

- **Tabular overview of clinical studies**

Study ID	Study Title and Description	Study Objectives or Outcomes	Patient, Study Participant, or Tumour Population	Number of Treated Participants
Registration Study				
LOXO-RET-17001 (J2G-OX-JZJA; LIBRETTO-001)	A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumours, Including *RET* Fusion-Positive Solid Tumours, Medullary Thyroid Cancer, and Other Tumours with *RET* Activation. Key design features: • multicentre • multicohort • open label • single arm, and • dose escalation followed by dose expansion.	**Phase 1** ***Primary objective***: To determine MTD and/or RP2D. ***Secondary objectives***: To assess • safety and tolerability • PK, and • ORR. **Phase 2** ***Primary objective***: To assess ORR by IRC. ***Secondary objectives***: To assess • ORR by IA • DOR, TTBR, PFS, CBR, best change in tumour size by IRC and IA • CNS ORR and DOR by IRC • OS • safety and tolerability, and • PK.	*RET* fusion-positive NSCLC	360
			RET-mutant MTC	319
			RET fusion-positive thyroid cancer	56
			RET fusion-positive other cancers	45
			Other cancers	26
			Total[a]	806

- LIBRETTO-121,a multicentre, open-label, Phase 1/2 study in paediatric patients with an advanced solid or primary central nervous system tumour harbouring, an activating RET alteration.

2.3.2. Pharmacokinetics

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

In Europe selpercatinib is available as two strengths of hard capsules, 40 and 80 mg.

Selpercatinib is orally administered 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.

The pharmacokinetic (PK) properties of selpercatinib were sufficiently characterized in the initial MAA (EMEA/H/C/005375/0000)

The PK data provided in support of this submission includes:

- Descriptive analysis of selpercatinib non-compartmental PK data from adult patients with RET fusion-positive TC (with or without previous systemic therapy other than radioactive iodine) enrolled in the pivotal study **LOXO-RET-17001** (LIBRETTO-001) as of the cut-off date (10 June 2021) and,

- Summary of steady state PK parameters (Cmax and AUC0-24h) in 4 paediatric patients (aged 13 months through 10 years) treated with dose of 90 mg/m2 BID up to a maximum of 160 mg BID in the setting of single-patient compassionate use protocols.

No PK data were available from the dedicated paediatric study LIBRETTO-121.

Pharmacokinetic in target populations

PK data in Adult patients with thyroid cancer

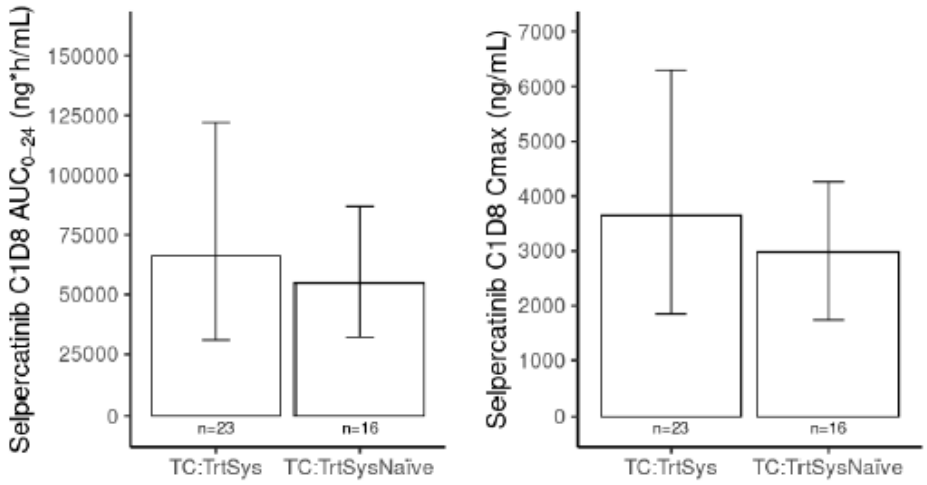
PK data from study **LOXO-RET-17001** as of the data cutoff of 10 June 2021 were previously reported in procedures EMEA/H/C/005375/II/0011 and EMEA/H/C/005375/II/0014. Of the 757 patients with evaluable PK data, 51had TC. Table **4**. presents the available steady-state exposure (AUC0-24 and Cmax at steady state [C1D8]) of selpercatinib for patients with TC taking 160 mg selpercatinib BID with (TC:TrtSys) or without (TC:TrtSysnaïve; Naïve patients) a previous systemic therapy.

Table 4. Steady-state (C1D8) PK parameters of selpercatinib in patients with TC taking 160 mg BID of capsule formulation

	TC:TrtSysNaïve		TC:TrtSys	
	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)
N	16	16	23	23
Geometric mean	2880	52900	3400	61000
Geometric CV%	28	28	40	44
95% CI	1740, 4260	32200, 86900	1850, 6300	31100, 122000

Abbreviations: AUC0-24 = area under the plasma concentration-time curve from time 0 to 24 hours; BID = twice daily; CI = confidence interval; Cmax = maximum plasma concentration; CV = coefficient of variation; N =number of samples; RAI = radioactive iodine; TC = thyroid cancer; TrtSys = Patients Previously Treated with Systemic Therapy; TrtSysNaïve = Patients Not Previously Treated with Systemic Therapy other than RAI. Sources: Data available from 09 May 2017 to 10 June 2021

Figure 1. Bar charts of plasma selpercatinib Cmax and AUC0-24 following selpercatinib 160 mg BID administrations (C1D8) in patients with RET Fusion-Positive thyroid cancer



PK data in Adolescent patients with thyroid cancer

At the time of the current submission, no data in adolescent patients were present in the ongoing pivotal studyLOXO-RET-17001 LIBRETTO-001 in the advanced RET fusion-positive TC population.

As of 08 May 2022, 6 patients with RET fusion-positive TC aged 12 to 18 years have been treated in Study LIBRETTO 121 however no PK data were analysed and available: These include:

- 4 patients aged 12 years
- 1 patient aged 15 years, and
- 1 patient aged 17 years.

During the procedure PK data from 19 evaluable paediatric patients ≥ 12 years old were provided from *the ongoing pivotal paediatric Study LIBRETTO-121 (data available up 13 January 2023)*

Table 5. Selpercatinib Pharmocokinatics and Demographics in paediatric Patients in study LIBRETTO-121 Aged 12 years and older Stratified by Actual administered dose amount at cycle 1 Day 8

	Geometric Mean (%CV)		
	LIBRETTO-121 Patients ≥ 12 Years N = 9	**LIBRETTO-121 Patients ≥ 12 Years** N = 5	**LIBRETTO-121 Patients ≥ 12 Years** N = 5
Dose		**92 mg/m^2 BID**	
Actual amount administered	**160 mg BID**	**140 mg BID**	**120 mg BID**
Age[a]	16 (12-20)	15 (13-19)	13 (12-20)
Weight[a,b]	63.5 (56.1-97.7)	51.1 (48.3-54.7)	42.6 (38.6-46.1)
C_{max} (ng/mL)	3310 (28)	3580 (23)	3910 (36)
AUC(0-24)(h.ng/mL)	52900 (46)	60000 (20)	61800 (42)

Abbreviations: AUC(0-24)=area under the plasma concentration-time curve from time 0 to 24 hours; BID = twice daily; C_{max} = maximum plasma concentration; CV = coefficient of variation; N = number of patients.

[a] Median (minimum – maximum).

[b] Based on baseline value at visit Cycle 1 Day 1 (C1D1). Weights at screening were substituted for 2 patients who were missing weight measurements at C1D1.

The applicant provided PK data in 4 paediatric patients (aged 13 months through 10 years) treated in the setting of single-patient compassionate use protocols and who received the dose of 90 mg/m2 BID up to a maximum of 160 mg BID.

According to the Applicant, steady-state exposure of these paediatric patients *Table 6* were well within the variability band of exposures in adults patients in LIBRETTO-001 given 160 mg BID (geometric mean Cmax of 3050 ng/mL and geometric CV% of 51.4%, geometric mean AUC0-24 of 52600 ng*h/mL, and geometric CV% 55.5%).

Table 6. Pharmacokinetic Parameters of Selpercatinib in Cancer Patients Treated Through Single-Patient Compassionate Use Protocols – Paediatric

Patient Age	Dose	Day 8 (Steady-State) Exposure	
		C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)
8 years	80 mg BID	4970	63300
13 months	44.1 mg BID	5280	85600
10 years	160 mg BID	3810	59800
21 months	42 mg BID	3350	43200

Pharmacokinetic interaction studies

No new data have been submitted as part of this application**.**

2.3.3. Pharmacodynamics

Mechanism of action

No new data have been submitted as part of this application.

Primary and secondary pharmacology

No new data have been submitted as part of this application.

2.3.4. Discussion on clinical pharmacology

In the current submission, the applicant claims an extension of indication for selpercatinib in advanced RET fusion-positive TC to include treatment in a first-line setting and to include adolescent patients ≥12 years.

For the purpose of first-line treatment in adults, updated PK data in adult TC patients from the pivotal study LOXO-RET-17001were provided. Of the 757 patients with evaluable PK data in the ongoing pivotal study LOXO-RET-17001 (data available up to 10 June 2021), 51 patients had TC but only PK data from 39 patients were provided.

Using a Noncompartmental analysis (NCA) approach, PK exposure parameters at steady-state (AUC0-24h, Cmax) were determined from RET fusion-positive TC patients naïve to previous systemic therapy (n=16) and TC patients previously treated with systemic therapy (n=23). Overall**,** steady state systemic exposure of selpercatinib in patients with TC naïve vs those with prior systemic therapy appears to be similar. The geometric means of steady state PK parameters on selpercatinib in naïve TC patients (n=16, Cmax = 2880 ng/mL and AUC0-24h = 52900 ng.h/mL) were slightly lower (15 and 13%, respectively) than those in TC patients with prior systemic therapy (n=23, Cmax = 3400 ng/mL and AUC0-24h = 61000 ng.h/mL) and their 95% CI substantially overlapped.

The provided PK results in TC patients indicate that steady-state PK following 160 mg BID administration for patients with RET fusion-positive TC appears overall similar to those already reported for patients with NSCLC and MTC (geometric means of Cmax between 2630 and 3600 ng/mL and AUC0-24h between 45500 to 64000 ng.h/mL). Therefore from a PK perspective, the recommendation of the same dosing

regimen, as reported in the current product information, for the first-line setting in patients with TC is supported.

For the purpose of extension indication in adolescent patients the PK data from 19 evaluable paediatric patients with age 12 years or older (data available up 13 January 2023) were provided from the ongoing pivotal paediatric Study LIBRETTO-121. Using the NCA approach, , the geometric means of steady-state (C1D8) selpercatinib systemic exposures in adolescents ≥12 years old receiving a 92 mg/m2 dosing (n= 19, Cmax = 3530 ng/mL and AUC0-24h = 57000 ng.h/mL) were in a similar range (15 and 7%, respectively higher) compared to those observed in adult patients with cancer treated with 160 mg BID in the pivotal Study LOXO-RET-17001 (n= 646, Cmax = 3060 ng/mL and AUC0-24h = 53000 ng.h/mL) and the distributions of Cmax and AUC0-24h largely overlapped. Importantly, the 92 mg/m2 BID dosing used in pediatric patients ≥12 years old turns to nominal administered doses of 120 to 160 mg BID, which is in line with the actually recommended doses in adults.

Furthermore, when analysed by dose level, paediatric patients ≥12 years old, body weight <50 kg, and administered dose of 120 mg BID (n= 5) had comparable systemic exposures at steady state (Cmax = 3910ng/mL and AUC0-24h = 61800 ng.h/mL) with paediatric patients ≥12 years old, body weight >50 kg, and administered dose of 160 mg BID (n = 9, Cmax = 3310 ng/mL and AUC0-24h = 52900 ng.h/mL) as well adult patients with 160 mg BID. Overall, based on these results, the systemic exposure on selpercatinib at steady state in adolescent patients ≥12 years old receiving the actual recommended weight-based dosing regimen for adults [120 mg BID in patients below 50 kg and 160 mg BID in patients who are at least 50 kg] is expected to be similar to that observed in the already approved adult patients (160 mg BID).

2.3.5. Conclusions on clinical pharmacology

No significant difference in PK characteristics of selpercatinib is observed in naïve RET fusion-positive TC patients compared to those previously treated with systemic therapy. Therefore, from a PK perspective, the claim to extend selpercatinib indication to first-line setting in adult TC patients is agreed.

Based on interim PK from 19 evaluable paediatric patients with age 12 years or older (data available up 13 January 2023) issued from the ongoing pivotal pediatric Study LIBRETTO-121 data, the systemic exposure on selpercatinib at steady state in adolescent patients ≥12 years old administered the actual recommended weight-based dosing regimen in adults was found to be in as similar range to that observed in adult patients with cancer. Therefore, from a PK perspective, the claim to extend selpercatinib indication to adolescents ≥12 years old is agreed.

2.4. Clinical efficacy

2.4.1. Main study(ies)

Title of Study

LIBRETTO-001

Methods

LIBRETTO-001 is a first in human Phase 1/2, multicentre, single-arm, multicohort, open-label, dose-escalation study in patients aged 12 years or older with advanced solid tumours, including RET fusion-positive solid tumours, RET-mutant MTC, and other tumours with RET activation.

As a note, the LIBRETTO-001 study has been the basis to support the following indications:

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 thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib*

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC).

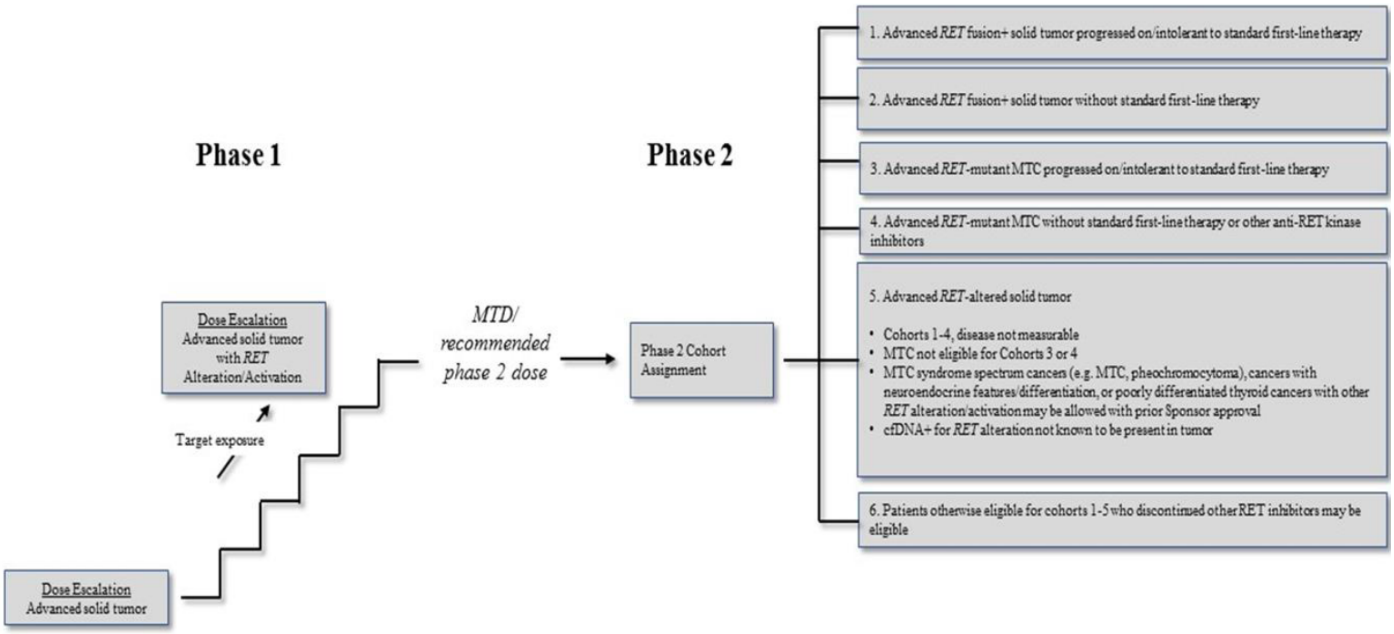
The study includes 2 parts:

- Phase 1 (dose escalation and expansion) and

- Phase 2 (dose expansion).

After completion of the Phase 1 dose-escalation portion, the Phase 2 dose expansion to enrol patients with RET fusion-positive or RET-mutant cancers was initiated. Phase 2 cohorts were defined based on disease characteristics and patient history, for example, measurable or non-measurable disease, prior systemic therapy or systemic therapy naïve. Patients contributing to the RET fusion-positive TC population come from both Phases 1 and Phase 2 portions of the study. Assessments and by IRC (Independent Review Committee) and by Investigator were planned to be included.

Figure 2. Study design as of protocol version 9.0.



Abbreviations: cfDNA = circulating free tumour DNA; MTC = medullary thyroid cancer; MTD = maximum tolerated dose; RET = REarranged during Transfection.

Phase I dose escalation part

Study participants

Eligibility criteria at the time of this interim report was specified as per protocol Version 9.0. (15 June 2021 data cut-off).

Main selection criteria for phase 1 were:

Inclusion Criteria

● Patients with a locally advanced or metastatic solid tumor who:

- have progressed on or are intolerant to standard therapy, or

- no standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or

- decline standard therapy.

● Prior MKIs with anti-RET activity were allowed.

● A RET gene alteration was not required initially. Once adequate PK exposure was achieved, evidence of RET gene alteration in tumor and/or blood was required (e.g., gene rearrangement and/or mutation, excluding synonymous, frameshift, or nonsense mutations) as identified through molecular assays, as performed for clinical evaluation. The RET alteration result should have been generated from a laboratory with CLIA, ISO/IEC, CAP or other similar certification. The Sponsor should have been contacted to discuss test results from labs where such certification was not clearly demonstrated to determine eligibility.

● Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumor type.

● At least 18 years of age.

- For countries and sites where approved, patients as young as 12 years of age could be enrolled.

• Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 (age ≥ 16 years) or Lansky Performance Score (LPS) ≥ 40% (age < 16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment.

● Life expectancy of at least 3 months.

Exclusion Criteria for Phase 1

- an additional validated oncogenic driver that could cause resistance to selpercatinib treatment.

Outcomes/endpoints

Phase 1 primary objective

The primary objective of the Phase 1 portion of LIBRETTO-001 was to determine the MTD and recommended Phase 2 dose of selpercatinib. A dose of 160 mg BID was selected for Phase 2.(please ref to sectino 2.3.4)

Phase 2 dose expansion part

Inclusion Criteria for Phase 2

Inclusion Criteria are the same as for Phase 1, with the following modifications:

● Cohorts 1 and 3: failed or intolerant to standard of care; Cohorts 2 and 4: without prior standard-first line therapy.

Table 7. Standard of Care Therapies for Cohorts 1-4

COHORT	THERAPY
Cohort 1: *RET* Fusion-Positive Solid Tumor	NSCLC: platinum-based chemotherapy (or other chemotherapy if not eligible for platinum) or PD-1/PD-L1 immunotherapy or both Thyroid: sorafenib and/or lenvatinib, patients must also be radioactive iodine-refractory as appropriate Colorectal: fluoropyrimidine-based chemotherapy, with or without anti-VEGF-directed therapy or anti-EGFR-directed therapy as appropriate for the disease Pancreas: fluoropyrimidine-based, gemcitabine-based, or S-1 chemotherapy Breast: anthracycline, taxane, HER2-directed therapy and/or hormonal therapy or other standard therapy appropriate for the disease Other: prior standard therapy for the disease
Cohort 2: *RET* Fusion-Positive Solid Tumor	Without prior standard-first line therapy, only if Inclusion Criteria 1 from Phase 1 is met: • no standard therapy exists, or • in the opinion of the Investigator is not a candidate for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or • decline standard therapy
Cohort 3: *RET*-mutant MTC	Cabozantinib or vandetanib or both agents
Cohort 4: *RET*-mutant MTC	Without prior standard-first line therapy, only if Inclusion Criteria 1 from Phase 1 is met: • no standard therapy exists, or • in the opinion of the Investigator is not a candidate for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or • decline standard therapy

● Cohorts 1-4: enrollment was to be restricted to patients with evidence of a RET gene alteration in tumor (i.e., not just blood) as defined in *Table 7*. However, a positive germline DNA test for a RET gene mutation as defined in *Table 7* was acceptable in the absence of tumor tissue testing for patients with MTC.

● Cohorts 1-4: at least one measurable lesion as defined by RECIST 1.1 or RANO, as appropriate to tumor type and not previously irradiated (unless PD for the irradiated lesion[s] has been radiographically documented).

● Cohort 4: radiographic Progression Disease within the previous 14 months.

● Cohort 6: patients otherwise eligible for Cohorts 1-5 who discontinued another selective RET inhibitor(s) due to intolerance may be eligible with prior Sponsor approval.

Exclusion Criteria for Phase 2

● Phase 2 Cohorts 1-4: an additional validated oncogenic driver that could cause resistance to selpercatinib treatment.

Treatments

The recommended Phase 2 dose of 160 mg twice daily (BID) was selected in Phase 1 and has been used as the starting dose for patients in the ongoing Phase 2 dose expansion.

Details of selpercatinib administration remained the same as for the authorized indication in second line of treatment of RET-fusion advance or metastatic TC.

Individual patients continued selpercatinib dosing until progressive disease, unacceptable toxicity, or other reason for treatment discontinuation.

Patients with progressive disease could continue selpercatinib if the patient was deriving clinical benefit from continuing selpercatinib, as determined by the Investigator and if continuation of selpercatinib was approved by the Sponsor.

Objectives

Please see the outcomes and endpoints section.

Outcomes/endpoints

The following table lists the objectives and endpoints for the Phase 2 part of the study as per protocol Version 9.0.

Table 8. Objectives and Endpoints for the Phase 2 part

Objectives (Phase 2)	Endpoints (Phase 2)
Primary	
• To assess the anti-tumour activity of selpercatinib in patients with *RET* fusion-positive TC	• ORR based on IRC assessment using RECIST v1.1
Secondary	
• To assess the anti-tumour activity of selpercatinib in patients with *RET* fusion-positive TC	• ORR based on Investigator assessment using RECIST v1.1 • TTR, TTBR, DoR, CBR based on IRC and Investigator assessment • PFS based on IRC and Investigator assessment, and • OS
• To determine the safety profile and tolerability of selpercatinib in patients with *RET* fusion-positive TC	• Safety per CTCAE (including but not limited to): frequency, severity, and relatedness of TEAEs, SAEs, deaths, and clinical laboratory abnormalities • changes in haematology and blood chemistry values • assessments of physical examinations • vital signs, and • ECGs

Objectives (Phase 2)	Endpoints (Phase 2)
• To characterise the PK properties of selpercatinib	• Plasma concentrations of selpercatinib and PK parameters, including, but not limited to, AUC_{0-24}, C_{max}, and T_{max}

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from 0 to 24 hours; CBR = clinical benefit rate; C_{max} = maximum observed drug concentration; CTCAE = Common Terminology Criteria for Adverse Events; DoR = duration of response; ECG = electrocardiogram; IRC = Independent Review Committee; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; RET = REarranged during Transfection; SAE = serious adverse event; TC = thyroid cancer; TEAE = treatment-emergent adverse event; T_{max} = time to maximum plasma concentration; TTBR = time to best response; TTR = time to response.

Sample size

For Phase 2, For Cohort 2 a true ORR of ≥ 55% was hypothesized when selpercatinib was administered to patients with RET fusion-positive solid tumors without prior standard first-line therapy. A sample size of 59 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 35%.

Randomisation

Not applicable, this is a single-arm study.

Blinding (masking)

Not applicable, this is an open-label study.

Statistical methods

The efficacy analyses was to be conducted on all treated patients unless otherwise specified.

Patients with RET fusion-positive TC who had received at least 1 dose of selpercatinib and achieved at least 6 months of potential follow-up time from the first dose of selpercatinib (or disease progression or death, whichever occurred first), as of 15 June 2021, were considered eligible for efficacy analyses. Response were to be assessed approximately every 2 months. Six (6) months of follow-up provides sufficient time for initial responses to be confirmed.

ORR was to be assessed using RECIST 1.1. The estimate of the ORR was to be calculated based on the maximum likelihood estimator (i.e., crude proportion of patients with best overall response of CR or PR that are confirmed based on RECIST 1.1). The estimate of the ORR was to be accompanied by 2-sided CIs with various coverage probabilities (e.g., 80%, 95%).

The analysis of ORR was to be conducted both by the responses determined by each Investigator and responses as determined by IRC.

This interim CSR follows the SAP Version 1.0 7 August 2019.

Measures to Minimise Bias

This study included an IRC for efficacy assessments in addition to the Investigator assessments. The primary radiography imaging files from LIBRETTO-001 were sent to a third-party vendor for central review.

Missing data

Unless noted otherwise, missing data was not to be imputed. All analyses were planned to be based on observed data only. The effective sample sizes at each assessment visit were planned to be based on the total number of patients with non-missing data for the parameter of interest at that visit.

This interim CSR follows the SAP Version 1.0 7 August 2019 which does not specify the analysis for the subset *RET* Fusion-Positive TC without prior systemic treatment.

Results

LIBRETTO-001 is currently ongoing and continues to enrol patients with advanced solid tumours.

Data presented below are from LIBRETTO-001, as of a data cutoff date of 15 June 2021 and data cutoff date of 13 January 2023, in patients with advanced or metastatic RET fusion-positive TC.

Participant flow

At the data cutoff date, 15 June 2021 921 patients were screened. Of these, 123 patients were screen failures, and 2 patients were in screening.

Overall, 796 patients from both Phase 1 cohorts and Phase 2 dose-expansion cohorts were treated with at least 1 dose of selpercatinib as of the data cut-off date.

54 patients with RET fusion-positive TC from Phase 1 and Phase 2 Cohorts 1, 2, 5, and 6 were considered as part of the TC safety analysis dataset.

The evaluation of efficacy consists of RET fusion-positive TC analysis sets includes patients enrolled into Phase 2 Cohorts 1, 2, and 5.

The efficacy analysis for RET fusion-positive TC primarily focused on:

1. patients not previously treated with systemic therapy other than RAI nr 16 (primary efficacy analysis set) and

2. patients previously treated with systemic therapy nr 30 (supportive efficacy analysis set).

A total of 46 patients with RET fusion-positive TC were considered eligible for efficacy analyses, among them 16 patients were not previously treated with systemic therapy other than RAI (TC:TrtSysNaïve)

Table 9. Description of Efficacy Analysis Sets (DCO 15 June 2021)

Set Name	Analysis Set	Analysis Set Description	Number of Patients per Analysis Set (Total TC Efficacy Evaluable Dataset N = 46)
Primary Efficacy Analysis Set			
TC:TrtSysNaïve	Patients Not Previously Treated with systemic therapy (lenvatinib, sorafenib) and/or other systemic therapy other than RAI	Include patients with *RET* fusion-positive TC that have had no prior systemic therapy (lenvatinib, sorafenib) and/or other systemic therapy other than RAI and met the criteria in footnote a.	N = 16
Secondary Efficacy Analysis Set			
TC:TrtSys	Patients Previously Treated with systemic therapy (lenvatinib, sorafenib) and/or other systemic therapy	Includes all patients with *RET* fusion-positive TC previously treated with systemic therapy (lenvatinib, sorafenib), or other systemic therapy and met the criteria in footnote a.	N = 30

Abbreviations: CLIA = Clinical Laboratory Improvement Amendments; N = number of patients; RAI = radioactive iodine; RECIST = Response Evaluation Criteria in Solid Tumors; RET = REarranged during Transfection; SAP = statistical analysis plan; SCE = Summary of Clinical Efficacy; TC = thyroid cancer; TC:TrtSys = Patients Previously Treated with Systemic Therapy; TC:TrtSysNaïve = Patients Not Previously Treated with Systemic Therapy other than RAI.

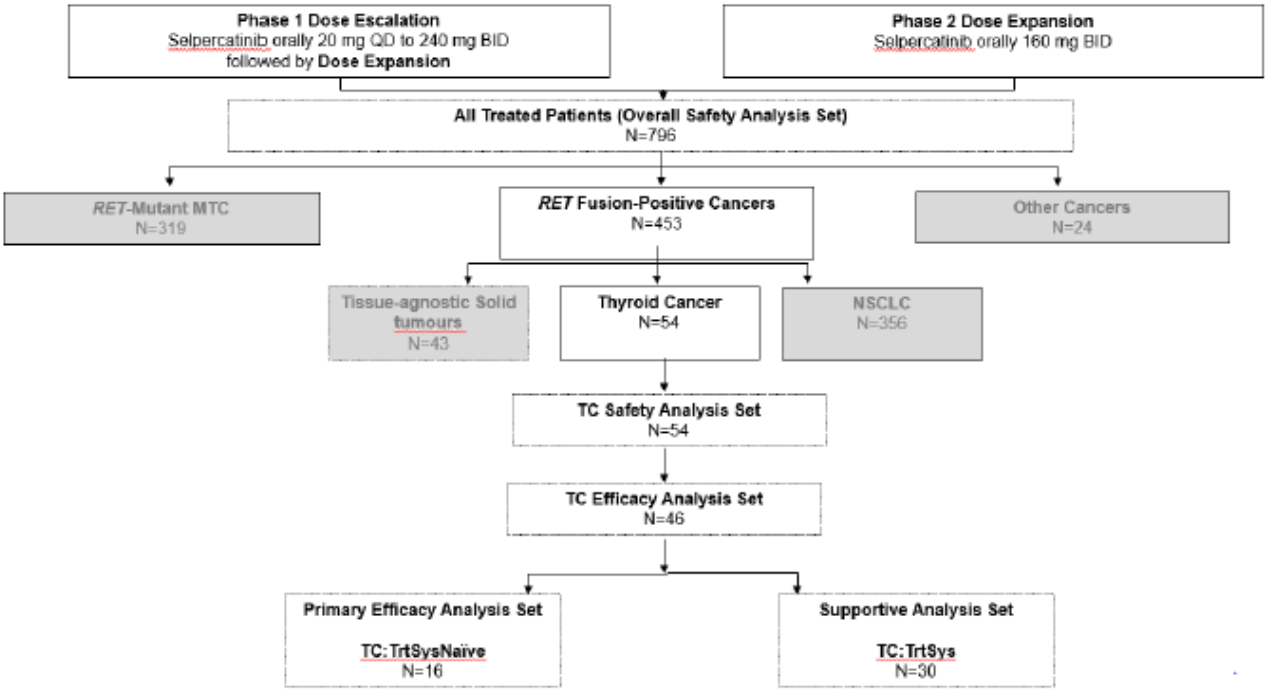
[a] Criteria for inclusion:

1. Evidence of a protocol-defined qualifying and definitive *RET* fusion prospectively identified based on a documented CLIA-certified (or equivalent ex-US) molecular pathology report.
2. Measurable disease by RECIST v1.1 by Investigator assessment. Patients in the Phase 1 dose-escalation portion of the study without measurable disease were considered. Refer to the SCE SAP for details.
3. Received 1 or more doses of selpercatinib.

Note: Evidence of a protocol-defined qualifying and definitive *RET* fusion prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with a *RET* fusion co-occurring with another validated oncogenic driver, as determined at the time of study enrolment by local testing, were included.

Measurable disease by RECIST v1.1 by Investigator assessment. Patients without measurable disease who were enrolled in Phase 1 dose escalation were included. Refer to the SCE SAP for details.

Figure 3. RET Fusion-Positive TC efficacy analysis and overall safety populations based on a data cutoff date of 15 June 2021.



Abbreviations: BID = twice daily; MTC = medullary thyroid cancer; N = number of patients; NSCLC = non-small-cell lung cancer; QD = once daily; RAI = radioactive iodine; RET = REarranged during Transfection; TC = thyroid cancer; **TC:TrtSys** = Patients Previously Treated with Systemic Therapy; **TC:TrtSysNaïve** = Patients Not Previously Treated with Systemic Therapy other than RAI.

Recruitment

This study was conducted at 80 centres that enrolled a total of 796 patients in North America, Asia Pacific, the European Union, and the Middle East.

The study initiation date (first participant first visit) is 09 May 2017.

The data cutoff date for interim analysis is 15 June 2021.

LIBRETTO-001 is currently ongoing and continues to enrol patients with advanced solid tumours.

No patients with RET fusion-positive TC aged 18 years or less were identified for participation in LIBRETTO-001.

Conduct of the study

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

Figure 4. Summary of Major Protocol Deviations TC Safety Population and Overall Safety Population (DCO 15 June 2021

Category	TC Safety Population N = 54 n (%)	Overall Safety Population N = 796 n (%)
Patients with major protocol deviations	5 (9.3)	161 (20.2)
Investigational product	2 (3.7)	61 (7.7)
Study procedure	0 (0.0)	43 (5.4)
SAE reporting	0 (0.0)	35 (4.4)
Restricted concomitant medication change	2 (3.7)	23 (2.9)
Inclusion criteria	0 (0.0)	16 (2.0)
Withdrawal criteria	1 (1.9)	11 (1.4)
Exclusion criteria	0 (0.0)	5 (0.6)
Informed consent	0 (0.0)	4 (0.5)

Abbreviations: N = number of patients; n = number of patients in the specific category; SAE = serious adverse event; TC = thyroid cancer.

Baseline data

Demographics

The following table presents the patients demographics by different efficacy analysis sets within the RET fusion-positive TC efficacy analysis population.

No patients with RET fusion-positive TC aged 18 years or less were identified for participation in LIBRETTO-001.

Table 10: Baseline Characteristics of patients with RET Fusion-Positive TC in LIBRETTO-001 (DCO 13 Jan 2023)

Characteristics	Treated (N= 41)	Naïve (N= 24)	Total Thyroid (N= 65)
Sex (n, %)			
Male	18 (43.9)	14 (58.3)	32 (49.2)
Female	23 (56.1)	10 (41.7)	33 (50.8)
Race (n, %)			
White	24 (58.5)	18 (75.0)	42 (64.6)
Black or African American	3 (7.3)	0 (0.0)	3 (4.6)
Asian	12 (29.3)	1 (4.2)	13 (20.0)
Other	2 (4.9)	3 (12.5)	5 (7.7)
Missing	0 (0.0)	2 (8.3)	2 (3.1)
Ethnicity (n, %)			
Hispanic or Latino	2 (4.9)	5 (20.8)	7 (10.8)
Not Hispanic or Latino	37 (90.2)	14 (58.3)	51 (78.5)
Missing	2 (4.9)	5 (20.8)	7 (10.8)
Age Group (n, %)			
18 to <45 years	9 (22.0)	5 (20.8)	14 (21.5)
45 to <65 years	15 (36.6)	8 (33.3)	23 (35.4)
65 to <75 years	7 (17.1)	9 (37.5)	16 (24.6)
75 to <85 years	9 (22.0)	2 (8.3)	11 (16.9)
85+ years	1 (2.4)	0 (0.0)	1 (1.5)
Age (years)			
N	41	24	65
Mean	59.1	57.1	58.4
Standard Deviation	16.71	16.47	16.52
Median	58.0	60.5	59.0
Minimum	25	20	20
Maximum	88	84	88
Height (cm)			
N	40	23	63
Mean	166.9	168.4	167.4
Standard Deviation	12.05	9.91	11.26
Median	167.0	171.0	169.0
Minimum	140	148	140
Maximum	197	186	197

Weight (kg)			
N	41	24	65
Mean	70.278	79.625	73.729
Standard Deviation	21.1714	21.1364	21.4792
Median	67.000	79.100	69.900
Minimum	40.00	38.90	38.90
Maximum	121.40	119.70	121.40
Body Mass Index (kg/m²)			
N	40	23	63
Mean	24.74	27.46	25.73
Standard Deviation	5.305	7.047	6.089
Median	23.42	27.21	25.28
Minimum	15.4	17.8	15.4
Maximum	35.6	51.8	51.8
ECOG Performance Status (n, %)			
0	11 (26.8)	14 (58.3)	25 (38.5)
1	27 (65.9)	9 (37.5)	36 (55.4)
2	3 (7.3)	1 (4.2)	4 (6.2)
Smoking History (n, %)			
Never Smoked	28 (68.3)	12 (50.0)	40 (61.5)
Former Smoker	13 (31.7)	10 (41.7)	23 (35.4)
Current Smoker	0 (0.0)	1 (4.2)	1 (1.5)
Missing	0 (0.0)	1 (4.2)	1 (1.5)
Phase 2 Cohort (n, %)			
Cohort 1	32 (78.0)	0 (0.0)	32 (49.2)
Cohort 2	5 (12.2)	18 (75.0)	23 (35.4)
Cohort 5	4 (9.8)	6 (25.0)	10 (15.4)

Percentage is calculated using the number of patients in the column heading as the denominator.
Eligible patients are defined as treated patients. Phase 2 patients enrolled in cohort 'COHORT 6 ELIGIBLE FOR COHORTS 1-5 BUT DISCONTINUED SELECTIVE RET INHIBITOR(S) DUE TO INTOLERANCE' are excluded.
Baseline is defined as the last measurement available prior to the first dose of LOXO-292.

Baseline Disease Characteristics

The following table presents the baseline disease characteristics by different analysis sets within the RET fusion-positive TC efficacy analysis population.

Table 11 Cancer History (RET Fusion-Positive TC) Efficacy Population DCO 13 Jan 2023)

Characteristics	Treated (N= 41)	Naïve (N= 24)	Total Thyroid (N= 65)
Primary Diagnosis (n, %)			
Thyroid	41 (100.0)	24 (100.0)	65 (100.0)
Papillary Thyroid Cancer	31 (75.6)	23 (95.8)	54 (83.1)
Poorly Differentiated Thyroid Cancer	5 (12.2)	1 (4.2)	6 (9.2)
Anaplastic Thyroid Cancer	4 (9.8)	0 (0.0)	4 (6.2)
Hurthle Cell Thyroid Cancer	1 (2.4)	0 (0.0)	1 (1.5)
Stage at Entry (n, %)			
II	1 (2.4)	0 (0.0)	1 (1.5)
III	2 (4.9)	0 (0.0)	2 (3.1)
IV	20 (48.8)	16 (66.7)	36 (55.4)
IVA	0 (0.0)	1 (4.2)	1 (1.5)
IVB	4 (9.8)	4 (16.7)	8 (12.3)
IVC	12 (29.3)	3 (12.5)	15 (23.1)
Missing	2 (4.9)	0 (0.0)	2 (3.1)
Months since Initial Diagnosis			
N	41	24	65
Mean	148.44	124.34	139.54
Standard Deviation	137.603	154.612	143.396
Median	102.10	65.85	94.10
Minimum	2.6	2.1	2.1
Maximum	562.7	574.9	574.9
History of Metastatic Disease (n, %)			
Yes	41 (100.0)	24 (100.0)	65 (100.0)
Months since Metastatic Disease			
N	41	24	65
Mean	88.18	69.14	81.15
Standard Deviation	110.456	84.830	101.475
Median	43.70	25.90	42.10
Minimum	1.9	1.1	1.1
Maximum	494.9	298.9	494.9

Prior Cancer Therapy

Of the 16 TC:TrtSysNaïve patients, 93.8% received prior RAI and no patients received other systemic therapy, including MKI therapy or chemotherapy.

The median number of prior rounds of RAI, was 1 (range, 0 to 4).

Table 12. Prior Cancer Therapy RET Fusion-Positive TC Efficacy Analysis Population Population (Data Cutoff: 13 January 2023)

Characteristics	Treated [5] (N= 41)	Naïve [5] (N= 24)	Total Thyroid (N= 65)
Received Prior Systemic Therapy (n, %)			
Yes	41 (100.0)	18 (75.0)	59 (90.8)
No	0 (0.0)	6 (25.0)	6 (9.2)
Type of Prior Systemic Therapy [1] (n, %)			
MKI	35 (85.4)	0 (0.0)	35 (53.8)
Cabozantinib	1 (2.4)	0 (0.0)	1 (1.5)
Vandetanib	1 (2.4)	0 (0.0)	1 (1.5)
Sorafenib	9 (22.0)	0 (0.0)	9 (13.8)
Lenvatinib	26 (63.4)	0 (0.0)	26 (40.0)
Both Sorafenib and Lenvatinib	4 (9.8)	0 (0.0)	4 (6.2)
Other MKIs [2]	7 (17.1)	0 (0.0)	7 (10.8)
Chemotherapy	8 (19.5)	0 (0.0)	8 (12.3)
Platinum Chemotherapy	4 (9.8)	0 (0.0)	4 (6.2)
Taxane Chemotherapy	5 (12.2)	0 (0.0)	5 (7.7)
Number of Prior Systemic Regimens (n, %)			
0	0 (0.0)	6 (25.0)	6 (9.2)
1	10 (24.4)	10 (41.7)	20 (30.8)
2	8 (19.5)	3 (12.5)	11 (16.9)
3 or more	23 (56.1)	5 (20.8)	28 (43.1)
Number of Prior Systemic Regimens			
N	41	24	65
Mean	3.1	1.5	2.5
Standard Deviation	1.86	1.41	1.87
Median	3.0	1.0	2.0
Minimum	1	0	0
Maximum	7	5	7
Type of Prior Systemic Therapy [1] (n, %)			
Immunotherapy	3 (7.3)	0 (0.0)	3 (4.6)
Anti-PD1/PD-L1 Therapy	3 (7.3)	0 (0.0)	3 (4.6)
Anti CTLA4 Therapy	0 (0.0)	0 (0.0)	0 (0.0)
Other	30 (73.2)	18 (75.0)	48 (73.8)
Radioactive Iodine	30 (73.2)	18 (75.0)	48 (73.8)
mTOR Inhibitor	2 (4.9)	0 (0.0)	2 (3.1)
EGRF Inhibitor	1 (2.4)	0 (0.0)	1 (1.5)
VEGF/VEGFR Inhibitor	0 (0.0)	0 (0.0)	0 (0.0)
Hormonal Therapy	0 (0.0)	0 (0.0)	0 (0.0)
Selective RET Inhibitor	0 (0.0)	0 (0.0)	0 (0.0)
Other Systemic Therapy [3]	4 (9.8)	0 (0.0)	4 (6.2)
Best Response to Last Systemic Treatment (n, %)			
Complete Response	0 (0.0)	1 (4.2)	1 (1.5)
Partial Response	8 (19.5)	0 (0.0)	8 (12.3)
Stable Disease	16 (39.0)	3 (12.5)	19 (29.2)
Progressive Disease	9 (22.0)	2 (8.3)	11 (16.9)
Not Evaluated	7 (17.1)	12 (50.0)	19 (29.2)
Unknown [4]	1 (2.4)	6 (25.0)	7 (10.8)
Prior Radiotherapy (n, %)			
Yes	20 (48.8)	10 (41.7)	30 (46.2)
No	21 (51.2)	14 (58.3)	35 (53.8)
Prior Cancer-Related Surgery (n, %)			
Yes	34 (82.9)	23 (95.8)	57 (87.7)
No	7 (17.1)	1 (4.2)	8 (12.3)

Percentage is calculated based on the number of patients in the column heading as the denominator.
Eligible patients are defined as treated patients. Phase 2 patients enrolled in cohort 'COHORT 6 ELIGIBLE FOR COHORTS 1-5 BUT DISCONTINUED SELECTIVE RET INHIBITOR(S) DUE TO INTOLERANCE' are excluded.
Stable Disease includes Non-CR/Non-PD.
* Indicates SD lasting >= 16 weeks following initiation of LOXO-292 until the criteria for disease progression was first met.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] 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.
[3] 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 (SD*). Stable disease was measured from the date of the first dose LOXO-292 until the criteria for disease progression was first met.
[4] Disease Control Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or stable disease (SD).
[5] 95% confidence interval was calculated using Clopper-Pearson method.

Numbers analysed

As of 15 June 2021, of the 46 efficacy-eligible patients with RET fusion-positive TC, 31 (67.4%) were still on treatment.

Of the 16 TC:TrtSysNaïve patients, 81.3% were still on treatment. The main reason for treatment discontinuation was:

- progressive disease (1 [6.3%]),
- withdrawal of consent (1 [6.3%]), or
- other (1 [6.3%]): withdrawal of consent for greater convenience.

Table 13. Summary of Disposition RET Fusion-Positive TC Efficacy Analysis Population (Data Cutoff: 15 June 2021)

n (%)	Primary Analysis Set TC:TrtSysNaïve N = 16	Supportive Analysis Set TC:TrtSys N = 30	Total TC N = 46
Treatment continuing	13 (81.3)	18 (60.0)	31 (67.4)
Treatment discontinued	3 (18.8)	12 (40.0)	15 (32.6)
Progressive disease	1 (6.3)	6 (20.0)	7 (15.2)
Adverse event	0 (0.0)	1 (3.3)	1 (2.2)
Requirement for alternative treatment per investigator	0 (0.0)	1 (3.3)	1 (2.2)
Significant non-compliance to protocol	0 (0.0)	2 (6.7)	2 (4.3)
Withdrawal of consent	1 (6.3)	2 (6.7)	3 (6.5)
Other	1 (6.3)	0 (0.0)	1 (2.2)
Treatment post-progression	2 (12.5)	11 (36.7)	13 (28.3)
Study status continuing	14 (87.5)	20 (66.7)	34 (73.9)
Study status discontinued	2 (12.5)	10 (33.3)	12 (26.1)
Withdrawal of consent	1 (6.3)	2 (6.7)	3 (6.5)
Death	1 (6.3)	7 (23.3)	8 (17.4)
Other	0 (0.0)	1 (3.3)	1 (2.2)

Abbreviations: N = number of patients; n = number of patients in the specific category; RAI = radioactive iodine; RET = REarranged during Transfection; TC = thyroid cancer; **TC:TrtSys** = Patients Previously Treated with Systemic Therapy; **TC:TrtSysNaïve** = Patients Not Previously Treated with Systemic Therapy other than RAI.

The data of eight more TC:TrtSysNaïve patients were added to the number analized during the assessment with a DCO of 13 January 2023.

Outcomes and estimation

Outcomes data from Study LIBRETTO-001 submitted at the start of the current procedure (Data cutoff date of 21 June 2021) are presented below along with efficacy data cutoff of 13 January 2023.

For the set of data with DCO 13 Jan 2023 a total of 66 patients with RET fusion-positive TC were treated with at least 1 dose of selpercatinib. Of the Thyroid Cancer Efficacy Population, 24 were TC:TrtSysNaïve patients.

Primary endpoint

***Objective Response Rate, DCO* 21 June 2021**

Table 14. Response Results RET Fusion-Positive TC Primary Efficacy Analysis Set (DCO 15 June 2021)

	TC:TrtSysNaïve N = 16	
	IRC Assessment	Investigator Assessment
Objective response rate[a]		
n (%)	15 (93.8)	13 (81.3)
95% CI[b]	69.8, 99.8	54.4, 96.0
Best overall response, n (%)		
CR	5 (31.3)	4 (25.0)
PR	10 (62.5)	9 (56.3)
SD	1 (6.3)	3 (18.8)
SD16+[c]	1 (6.3)	3 (18.8)
PD	0 (0.0)	0 (0.0)
Not evaluable	0 (0.0)	0 (0.0)
Clinical benefit rate (CR + PR + SD16+[c])		
n (%)	16 (100.0)	16 (100.0)
95% CI[b]	79.4, 100.0	79.4, 100.0
Disease control rate[h] (CR + PR + SD)		
n (%)	16 (100.0)	16 (100.0)
95% CI[b]	79.4, 100.0	79.4, 100.0
Duration of response		
Responders, n	15	13
Median in months (95% CI)[d,e]	NE (19.4, NE)	29.7 (13.1, NE)
Censored, n (%)	13 (86.7)	10 (76.9)
Reason censored, n (%)		
Alive without documented disease progression	10 (66.7)	8 (61.5)
Subsequent anti-cancer therapy or cancer-related surgery without documented PD	2 (13.3)	2 (15.4)
Died or documented PD after missing 2 or more consecutive visits	1 (6.7)	0 (0.0)
Rate (%) of duration of response[d,f]		
12 months (95% CI)	100.0 (NE, NE)	90.9 (50.8, 98.7)
24 months (95% CI)	77.9 (35.4, 94.2)	81.8 (44.7, 95.1)
36 months (95% CI)	NE (NE, NE)	NE (NE, NE)
Duration of follow-up (months)[e,g]		
Median	20.1	20.2
95% CI for median	9.3, 25.8	15.2, 25.8
25th, 75th percentiles	12.1, 25.8	15.7, 25.8

Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; N = number of patients in the population; n = number of patients per category; NE = not estimable; ORR = objective response rate; PD = progressive disease; PR = partial response; RAI = radioactive iodine; RET = REarranged during Transfection; SD = stable disease; SD16+ = stable disease lasting 16 or more weeks; TC:TrtSysNaïve = Patients Not Previously Treated with Systemic Therapy other than RAI.

[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 ≥28 days.

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

[c] SD16+ indicates SD lasting ≥16 weeks following initiation of selpercatinib.

[d] Estimate based on the Kaplan-Meier method.

[e] 95% CI was calculated using the Brookmeyer and Crowley method.

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

[g] Estimated based on the Reverse Kaplan-Meier method.

[h] Disease Control Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or SD.

Note: Censored patients are represented as a percentage of responders by IRC assessment (N = 15) and Investigator assessment (N = 13).

Data cutoff date: 15 June 2021.

Table 15. Response Results by IRC Assessment (RET Fusion-Positive TC) Efficacy Analysis Set TC:TrtSys and TC:TrtSysNaïve ***(DCO 13 Jan 2023)***

Data Cutoff Date	**13 January 2023 (N = 41)**	**13 January 2023 (N = 24)**
	TC:TrtSys	TC:TrtSysNaïve
Overall response rate[a,b]		
n (%)	35 (85.4)	23 (95.8)
95% CI	(70.8, 94.4)	(78.9, 99.9)
Best overall response, n (%)		
CR	5 (12.2)	5 (20.8)
PR	30 (73.2)	18 (75.0)
SD[c]	6 (14.6)	1 (4.2)
Progressive disease	0	0 (0.0)
Not evaluable	0	0 (0.0)
Clinical benefit rate (CR + PR + SD-16 weeks[c])[d]		
n (%)	41 (100.00)	24 (100.0)
95% CI[b]	(91.4, 100.0)	(85.8, 100.0)
Time to response		
Median in months	1.81	1.87
Duration of response[e,f]		
Responders, n	35	23
Censored, n (%)[g]	20 (57.1)	21 (91.3)
Median in months (95% CI)	26.71 (12.1, NE)	NE (42.8, NE)
Rate (%) of duration of response[e,g]		
≥6 months (95% CI)	91.2 (75.2, 97.1)	100.0 (NE, NE)
≥12 months (95% CI)	71.7 (52.4, 84.2)	100.0 (NE, NE)
Observed duration of response		
<6 months	5 (14.3)	2 (8.7)
>=6 to 12 months	11 (31.4)	6 (26.1)
>=12 to 18 months	6 (17.1)	4 (17.4)
>=18 to 24 months	2 (5.7)	1 (4.3)
>=24 months	11 (31.4)	10 (43.5)
Duration of follow-up (months)[f, i]		
Median	33.87	17.81

Abbreviations: CI = confidence interval; CR = complete response; IRC = independent review committee; n = number of patients per category; N = number of patients in population; NE = not estimable; ORR = objective response rate; PR = partial response; RET = REarranged during Transfection; SD = stable disease; TC = 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 of at least 28 days.

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

c SD indicates SD lasting at least 16 weeks following initiation of selpercatinib.

d Clinical benefit rate (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or SD lasting 16 or more weeks (SD-16 weeks). SD was measured from the date of the first dose of selpercatinib until the criteria for disease progression or death was first met.

e Estimate based on Kaplan-Meier method. + = censored observation.

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

Secondary endpoints

***Progression-Free Survival DCO* 21 June 2021**

Table 16. Progression-Free Survival Based on IRC and Investigator Assessment RET Fusion-Positive TC Primary Efficacy Analysis Set

Status	TC:TrtSysNaïve N = 16	
	IRC Assessment	Investigator Assessment
Progression status, n (%)		
Disease progression	3 (18.8)	3 (18.8)
Died (no disease progression beforehand)	0 (0.0)	0 (0.0)
Censored	13 (81.3)	13 (81.3)
Reason censored, n (%)		
Alive without documented disease progression	10 (62.5)	11 (68.8)
Subsequent anti-cancer therapy or cancer-related surgery without document progressive disease	2 (12.5)	2 (12.5)
Died or documented progressive disease after missing 2 or more consecutive visits	1 (6.3)	0 (0.0)
Progression-free survival (months)[a,b]		
Median	NE	NE
95% CI for median	19.3, NE	31.0, NE
Min-max	3.7+ - 33.0+	3.7+ - 33.1+
Duration of follow-up (months)[b,c]		
Median	22.1	23.9
95% CI for median	17.0, 27.6	17.0, 27.9
25th, 75th percentiles	17.0-27.6	17.0-27.9
Rate (%) of progression-free survival[a,d]		
12 months (95% CI)	92.9 (59.1, 99.0)	92.9 (59.1, 99.0)
24 months (95% CI)	83.6 (48.0, 95.7)	84.4 (50.4, 95.9)

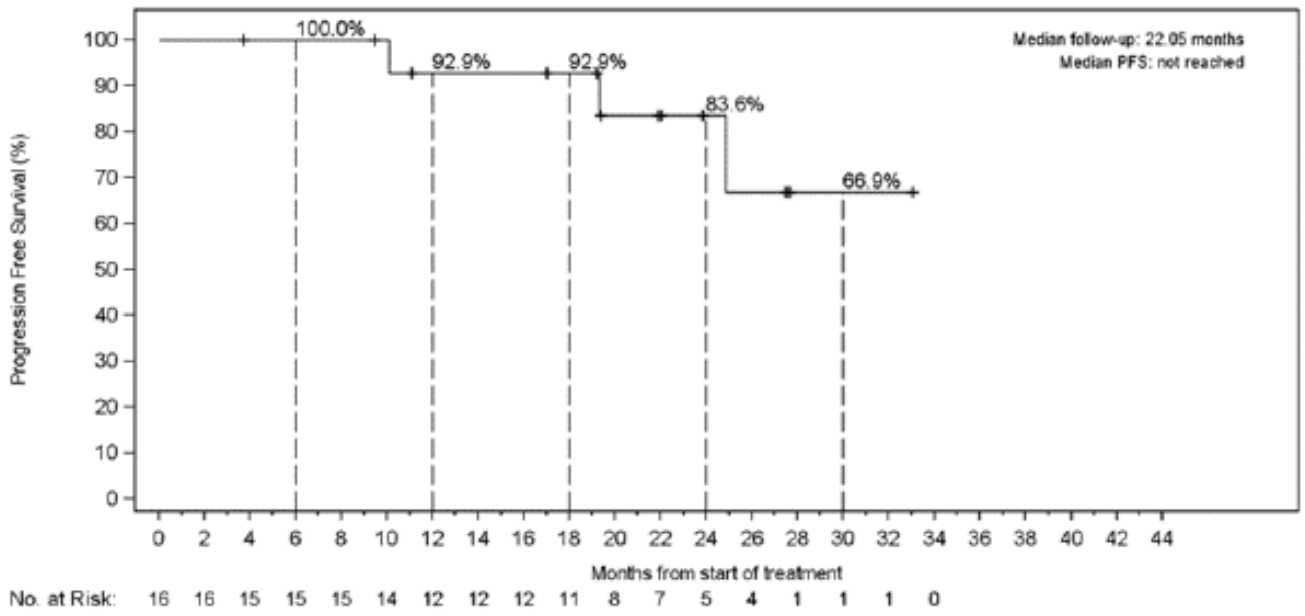
Abbreviations: CI = confidence interval; IRC = Independent Review Committee; N = number of patients; n = number of patients in the specific category; NE = not estimable; max = maximum; min = minimum; RAI = radioactive iodine; RET = REarranged during Transfection; TC = thyroid cancer; TC:TrtSysNaïve = Patients Not Previously Treated with Systemic Therapy other than RAI.

a Estimate based on the Kaplan-Meier method. + = censored observation.

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

c Estimate based on the Reverse Kaplan-Meier method.

Figure 5. Kaplan-Meier plot for progression-free survival based on IRC assessments RET Fusion-Positive TC Efficacy Analysis Set.



Abbreviations: + = censored observation; IRC = Independent Review Committee; No. = number; PFS = progression-free survival; RET = REarranged during Transfection; TC = thyroid cancer.

Progression-Free Survival DCO 13 Jan 2023

Table 17. Progression-Free Survival (RET Fusion-Positive TC) TC:TrtSys and TC:TrtSysNaïve DCO 13 Jan 2023

Data Cutoff Date	**13 January 2023**	
Population	TC:TrtSys	TC:TrtSysNaïve
N	41	24
Duration of progression-free survival (months)		
Median[a]	27.4	NE
95% CI[c]	14.5, NE	44.2, NE
Minimum, maximum	3.5, 60.5+	3.7+, 52.4+
Rate (%) of PFS		
≥12 months[a]	70.6	95.2
95% CI[c]	(53.2, 82.6)	(70.7,99.3)
Duration of PFS follow-up (months)		
Median[b]	30.39	24.94
25th, 75th percentiles	16.5, 41.1	11.2, 44.0

Abbreviations: CI = confidence interval; CR = complete response; n = number of patients per category; N = number of patients in population; NE = not estimable; ORR = objective response rate; PFS = progression-free survival; PR = partial response; RET = REarranged during Transfection; SD = stable disease; TC = thyroid cancer.

a Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.

b Estimate based on Reverse Kaplan-Meier method.

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

Overall Survival

Median OS was NE with a median follow-up time of 22.8 months (95% CI: 19.8, 29.4). The rate of OS at 12 months was 100.0% (95% CI: NE, NE) and at 24 months was 92.3% (95% CI: 56.6, 98.9).

*Table 18. Overall Survival RET Fusion-Positive TC Primary Efficacy Analysis Set **DCO** 21 June 2021*

	TC:TrtSysNaïve N = 16
Survival status, n (%)	
Died	1 (6.3)
Censored	15 (93.8)
Overall survival (months)[a,b]	
Median	NE
95% CI for median	NE, NE
Min-max	10.2+ - 35.6+
Duration of follow-up (months)[b,c]	
Median	22.8
95% CI for median	19.8, 29.4
25th, 75th percentiles	19.8, 29.4
Rate (%) of overall survival[a,d]	
12 months (95% CI)	100.0 (NE, NE)
24 months (95% CI)	92.3 (56.6, 98.9)

Abbreviations: CI = confidence interval; max = maximum; min = minimum; N = number of patients; n = number of patients in the specified category; NE = not estimable; RAI = radioactive iodine; RET = REarranged during Transfection; TC:TrtSysNaïve = Patients Not Previously Treated with Systemic Therapy other than RAI.

a Estimate based on the Kaplan-Meier method. + = censored observation

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

c Estimate based on the Reverse Kaplan-Meier method.

d 95% CI was calculated using the Greenwood's formula.

Note: Status as of the last contact on or before 15 June 2021.

Data cutoff date: 15 June 2021.

Table 19. Overall Survival (RET Fusion-Positive TC) TC:TrtSys and TC:TrtSysNaïve DCO 13 Jan 2023

Data Cutoff Date	**13 January 2023**	
Population	TC:TrtSys	TC:TrtSysNaïve
N	41	24
Duration of OS (months)		
Median[a]	NE	NE
95% CI[b]	25.3, NE	NE, NE
Minimum, maximum	7.6+, 62.4+	8.3+, 54.5+
Rate (%) of OS		
≥12 months[a]	94.8	100.0
95% CI[c]	(80.7, 98.7)	(NE, NE)
Duration of OS follow-up (months)		
Median[a]	36.90	38.74
25th, 75th percentiles	21.5, 49.3	17.1, 47.2

Abbreviations: CI = confidence interval; N = number of patients; NE = not estimable; OS = overall survival; RAI = radioactive iodine; RET = REarranged during Transfection; TC = thyroid cancer; TrtSysNaïve = patients not previously treated with systemic therapy other than RAI.

a Estimate based on Kaplan-Meier method.

b 95% CI was calculated using Brookmeyer and Crowley method.

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

Note: + = censored observation.

***Time to Response and Time to Best Response DCO* 21 June 2021**

For the 15 responders in the RET fusion-positive TC Primary Efficacy Analysis Set (TC:TrtSysNaïve), the median TTR and TTBR by IRC assessment was 1.8 and 3.6 months, respectively.

Table 20. Time to Response and Time to Best Response Based on IRC and Investigator Assessments RET Fusion-Positive TC Primary Efficacy Analysis Set

	TC:TrtSysNaïve N = 16	
	IRC Assessment	Investigator Assessment
Patients with best response of confirmed CR or PR, n	15	13
Time to response (months)[a]		
Median	1.8	1.8
25th, 75th percentiles	1.8, 4.6	1.8, 1.9
Min-max	1.4-7.2	1.4-5.5
Time to response, n (%)		
<2 months	10 (66.7)	10 (76.9)
≥2 to <4 months	1 (6.7)	1 (7.7)
≥4 months	4 (26.7)	2 (15.4)
Time to best response (months)[b]		
Median	3.6	1.9
25th, 75th percentiles	1.8, 5.5	1.8, 5.5
Min-max	1.7-13.8	1.4-14.0
Time to best response, n (%)		
<2 months	7 (46.7)	8 (61.5)
≥2 to <4 months	3 (20.0)	0 (0.0)
≥4 months	5 (33.3)	5 (38.5)

Abbreviations: CR = complete response; IRC = Independent Review Committee; max = maximum; min = minimum; N = number of patients; n = number of patients in the specific category; PR = partial response; RAI = radioactive iodine; RET = REarranged during Transfection; TC = thyroid cancer; TC:TrtSysNaïve = Patients Not Previously Treated with Systemic Therapy other than RAI.

[a] Time to response is defined as the number of months elapsed between the date of the first dose of selpercatinib and the first documentation of overall response (CR or PR whichever occurred earlier) that was subsequently confirmed.

[b] Time to best response is defined as the number of months elapsed between the date of the first dose of selpercatinib and the first documentation of CR (if the patient's best response is confirmed CR) or PR (if the patient's best response is confirmed PR) that was subsequently confirmed.

Ancillary analyses

Subgroup analysis

The below table summarises the ORR and DoR by RET fusion partner genes based on IRC assessments in the TC:TrtSysNaïve population treated until 15 December 2020.

Table 21. Objective Response Rate and Duration of Response by RET Fusion Partner Gene Based on IRC Assessments

		ORR		DoR[a]	
	Patients (n)	Number of Responders (%)[b]	95% CI	Median (months)	95% CI
***RET* Fusion Partners**	16	15 (93.8)	69.8, 99.8	NR	19.4, NE
CCDC6	9	9 (100.0)	66.4, 100.0	NR	19.4, NE
NCOA4	5	4 (80.0)	28.4, 99.5	NR	14.8, NE
Other	2	2 (PR, PR)	NA	NR	NE, NE

Abbreviations: CI = confidence interval; DoR = duration of response; IRC = Independent Review Committee; PR = partial response, NA = not applicable, NE = not evaluable; NR = not reached; ORR = objective response rate; RET = REarranged during Transfection.

[a] Estimate based on the Kaplan-Meier method.

[b] Percentage is not calculated when patients (n) ≤2 and best overall response is shown instead.

Note: Percentage is calculated based on the number of patients in the denominator.

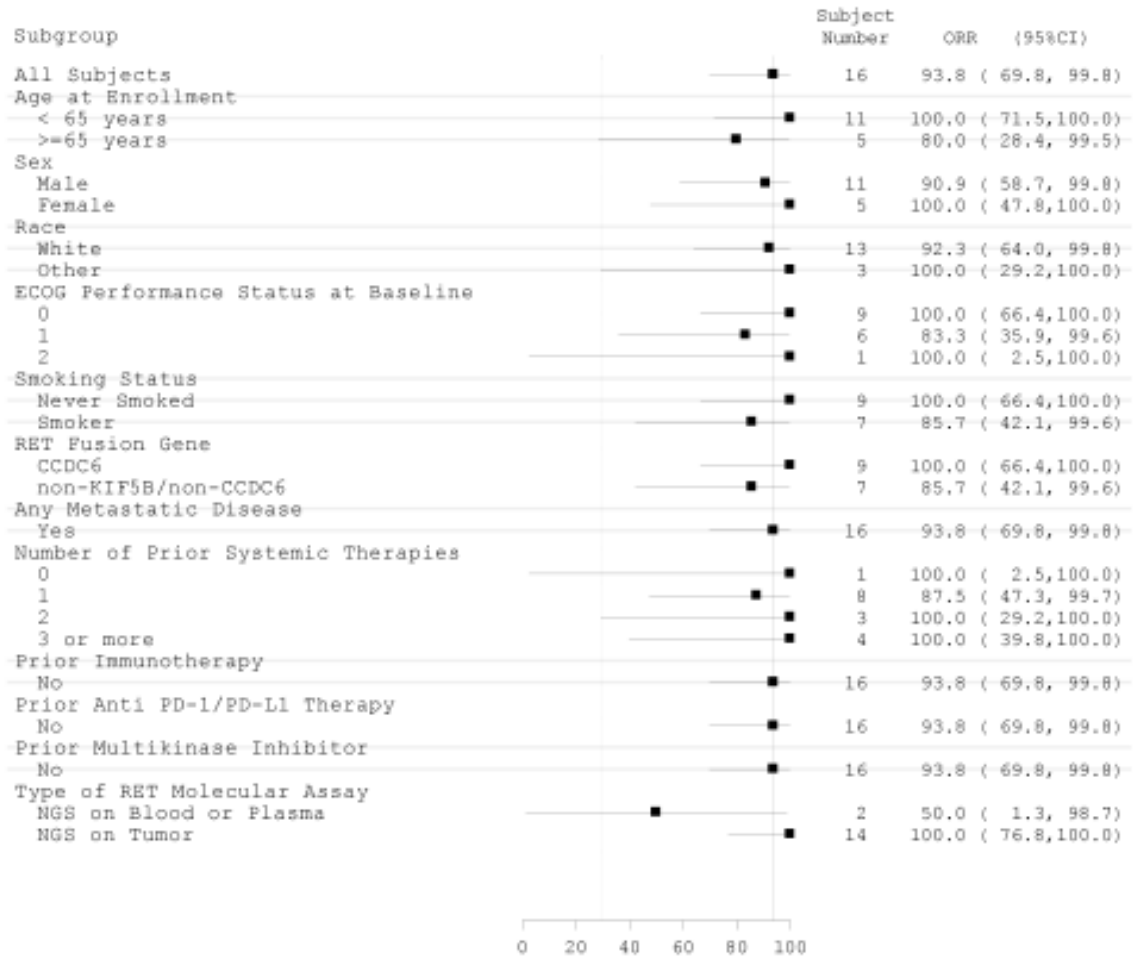
Patients may be counted in more than 1 *RET* fusion partner category.

Eligible patients are defined as patients treated on or before 15 December 2020.

Other: KIAA1217, TRIM24

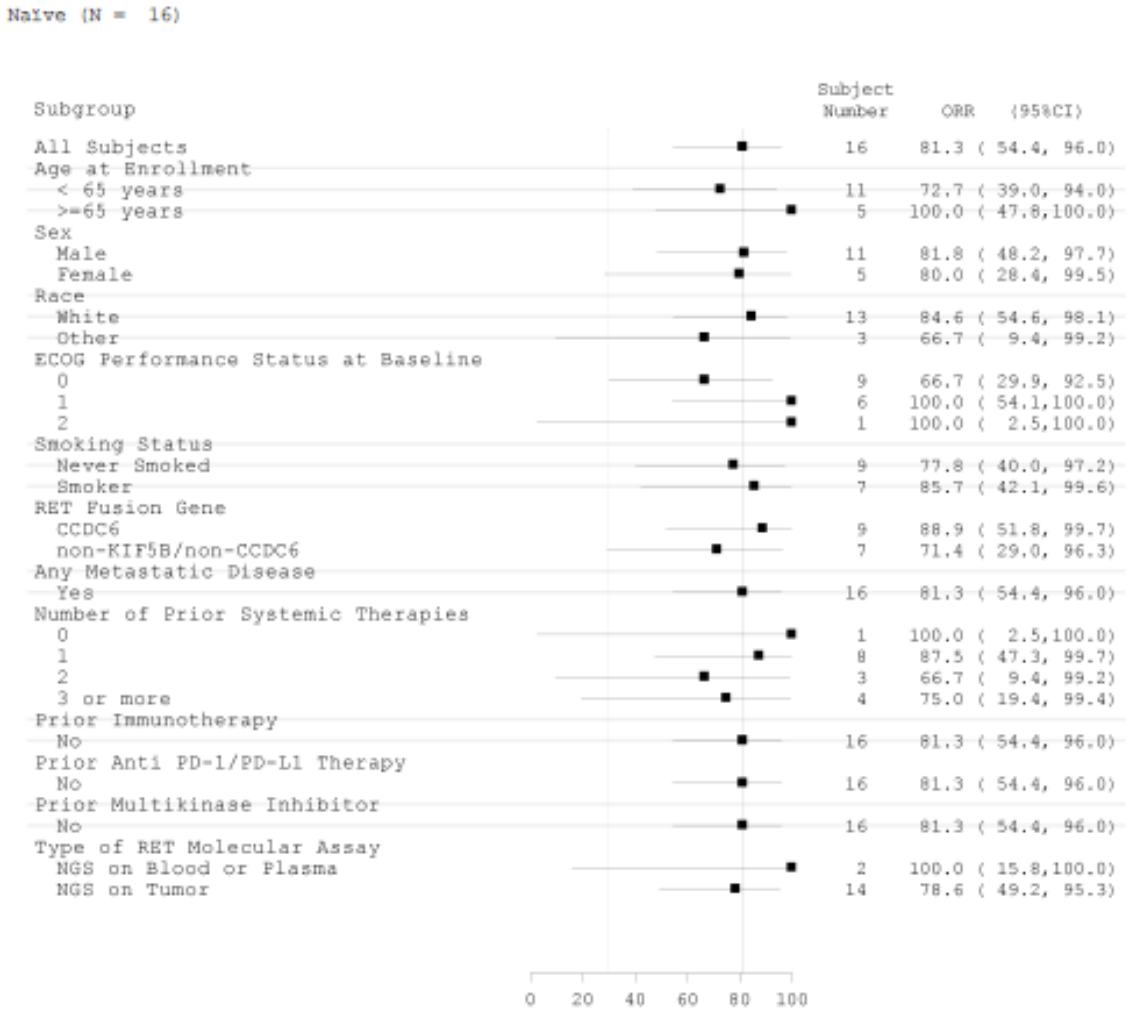
Figure 6. Forest Plot of Objective Response Rate in Special/Subgroup Populations Based on IRC Assessments Efficacy Eligible Subjects of RET Fusion Thyroid treated until 15 December 2020.

Naïve (N = 16)



Eligible patients are defined as patients treated on or before 15-DEC-2020. Phase 2 patients enrolled in cohort 'COHORT 6 ELIGIBLE FOR COHORTS 1-5 BUT DISCONTINUED SELECTIVE RET INHIBITOR(S) DUE TO
INTOLERANCE' are excluded.
Patients may be counted in more than one RET fusion gene subcategory.
Two-sided 95% exact binomial CI is calculated using the Clopper-Pearson method.
Dashed reference line = 30%, solid reference line = 93.8% (overall ORR).

Figure 7. Forest Plot of Objective Response Rate in Special/Subgroup Populations Based on Investigator Assessments Efficacy Eligible Subjects of RET Fusion Thyroid treated until 15 December 2020.



Eligible patients are defined as patients treated on or before 15-DEC-2020. Phase 2 patients enrolled in cohort 'COHORT 6 ELIGIBLE FOR COHORTS 1-5 BUT DISCONTINUED SELECTIVE RET INHIBITOR(S) DUE TO
INTOLERANCE' are excluded.
Patients may be counted in more than one RET fusion gene subcategory.
Two-sided 95% exact binomial CI is calculated using the Clopper-Pearson method.
Dashed reference line = 30%, solid reference line = 81.3% (overall ORR).

Supportive Efficacy Analysis Set from TC:TrtSys patients

Patients with RET Fusion-Positive TC Previously Treated with Systemic Therapy Other Than RAI

At the DCO 13 January 2023 TC:TrtSys patients (N = 41) had an ORR of 85.4% (95% CI: 70.8, 94.4). With a median response follow-up time of 33.9 months for the 35 responders, the median DOR estimated by the IRC was 26.7 months (95% CI: 12.1, NE), which demonstrates that selpercatinib provides robust and durable responses. The estimated rate of DOR was 71.7% at 12 months and 50.7% at 24 months. The median time to response by the IRC assessment was 1.8 months, with 71.4% of patients demonstrating an initial response at the first post-baseline radiographic assessment.

The median PFS estimate reached 27.4 months (95% CI: 14.5, NE), with a median follow-up of 30.4 months. The median OS was not reached.

Study: LIBRETTO-121

This is a multicenter, open-label, Phase 1/2 study in paediatric patients (paediatric patients ≥ 12 years of age and ≤ 21 years) with an advanced solid or primary CNS tumor harboring an activating RET alteration.

Objectives and endpoints

Table **1** summarizes the objectives and endpoints for the Phase 1/2 part of the study (interim report as per Protocol Version 7.0)

Table 22 Objectives and Endpoints

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 best overall response 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)

Objectives	Endpoints
○ 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 best overall response 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	• PFS (IRC and treating investigator) • OS • CBR (IRC and treating investigator)
• 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
• To characterize the PK properties of selpercatinib in pediatric patients	• 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

Main Inclusion/Exclusion Criteria

To be eligible for the study, patients must have

- been at least 6 months of age and 21 years of age or below at C1D1 with a locally advanced or metastatic solid or primary CNS tumor that had relapsed, progressed, or was nonresponsive to available therapies and/or for which no standard or available systemic curative therapy exists
- evidence of an activating RET gene alteration in tumor 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
- had measurable or nonmeasurable but evaluable disease
- had a Karnofsky (patients 16 years and older) or Lansky (patients younger than 16 years) performance score of at least 50
- had adequate hematologic status, and/or
- had adequate renal, hepatic/pancreatic function.

Patients were not eligible to be included in the study, if they

- underwent major surgery within 2 weeks prior to C1D1, and/or
- 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 hyperglycemia or hypocalcemia, or
  - ◇ hypersensitive to any of the components of the investigational agent, selpercatinib or Ora-Sweet® SF and OraPlus®.

Disposition of Participants

Table 23. Summary of Study and Treatment Disposition By Tumor Type All Enrolled Population Data Cutoff: 13 January 2023

Study Disposition	Overall Population (N = 31) n (%)	MTC Population (N = 14) n (%)	PTC Population (N = 10) n (%)	Other (N = 3) n (%)
Patients enrolled	31	14	10	3
Screen failure	4	0	0	0
Subjects treated	27 (100.0)	14 (100.0)	10 (100.0)	3 (100.0)
Treatment status				
On treatment	22 (81.5)	13 (19.2)	9 (90.0)	0
Discontinued	5 (18.5)	1 (7.1)	1 (10.0)	3 (100.0)
Reason for treatment discontinuation				
Progressive disease	3 (11.1)	0	0	3 (100.0)
Pregnancy	1 (3.7)	0	1 (10.0)	0
Significant noncompliance to protocol	1 (3.7)	1 (7.1)	0	0
Study status				
On study	24 (88.9)	14 (100.0)	10 (100.0)	0
Discontinued	3 (11.1)	0	0	3 (100.0)
Reasons for study discontinuation				
Death	3 (11.1)	0	0	3 (100.0)

Abbreviations: MTC = medullary thyroid cancer; n = number of patients in the specific category; N = number of patients; PTC = papillary thyroid cancer.

Number of Participants

Table 24 provides the number of participants included in each analysis population.

Table 24. Analysis Populations for Study LIBRETTO-121

Population	Description	N
Entered	Patients who signed the informed consent/assent document	31
Safety and Efficacy	All patients who received at least 1 dose of selpercatinib	27
MTC	*Includes patients with RET-mutant MTC*	*14*
PTC	*Includes patients with RET-fusion PTC*	*10*
Other	*Includes patients with RET-altered osteosarcoma, malignant peripheral nerve sheath tumor and rhabdomyosarcoma*	*3*

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

Demographic and Other Baseline Characteristics

Table 25. Summary of Patient Demographics by Tumor Type Safety Analysis Population Data Cutoff: 13 January 2023

Parameter	Overall Population (N = 27)	MTC Population (N = 14)	PTC Population (N = 10)	Other (N = 3)
Age (years, n)				
Median	13.0	14.0	13.5	13.0
Min-Max	2-20	2-20	12-20	5-15
Overall age group, n (%)				
6 months - <2 years	0	0	0	0
2 - <12 years	6 (22.2)	5 (35.7)	0	1 (33.3)
12 - <18 years	15 (55.6)	5 (35.7)	8 (80.0)	2 (66.7)
18 - 21 years	6 (22.2)	4 (28.6)	2 (20.0)	0
Sex, n (%)				
Male	16 (59.3)	9 (64.3)	6 (60.0)	1 (33.3)

Parameter	Overall Population (N = 27)	MTC Population (N = 14)	PTC Population (N = 10)	Other (N = 3)
Female	11 (40.7)	5 (35.7)	4 (40.0)	2 (66.7)
Race, n (%)				
White	14 (51.9)	10 (71.4)	4 (40.0)	0
Black or African American	3 (11.1)	2 (14.3)	0	1 (33.3)
Asian	7 (25.9)	0	5 (50.0)	2 (66.7)
Other	2 (7.4)	1 (7.1)	1 (10.0)	0
Missing	1 (3.7)	1 (7.1)	0	0
Ethnicity, n (%)				
Hispanic or Latino	5 (18.5)	2 (14.3)	3 (30.0)	0
Not Hispanic or Latino	20 (74.1)	10 (71.4)	7 (70.0)	3 (100.0)
Unknown	1 (3.7)	1 (7.1)	0	0
Missing	1 (3.7)	1 (7.1)	0	0
Body weight (kg)				
Mean	48.3	44.2	54.6	46.8
Median	48.5	46.1	48.4	54.7
Min-Max	10-98	10-93	43-98	17-69
Height (cm)				
Mean (SD)	155.0 (25.90)	153.6 (33.29)	160.6 (10.05)	142.6 (25.83)
Median	165.0	169.9	162.5	148.0
Min-Max	75-191	75-191	142-176	115-165
Body Surface Area (m^2)				
Mean (SD)	1.4 (0.42)	1.4 (0.49)	1.5 (0.26)	1.3 (0.54)
Median	1.5	1.5	1.5	1.5
Min-Max	0-2	0-2	1-2	1-2
Karnofsky/Lansky PS Status, n (%)				
Mean (SD)	89.3 (16.39)	88.6 (15.62)	93.0 (14.94)	80.0 (26.46)
Median	100.0	100.0	100.0	90.0
Min-Max	50-100	60-100	60-100	50-100

Abbreviations: Max = maximum; Min = minimum; MTC = medullary thyroid cancer; n = number of subjects in the specified category; N = number of subjects in safety population; PS = performance status; PTC = papillary thyroid cancer; SD = standard deviation.

Table 26. Baseline Disease Characteristics by Tumor Type Safety Analysis Population Data Cutoff: 13 January 2023

Parameter	Overall Population (N = 27) n (%)	MTC Population (N = 14) n (%)	PTC Population (N = 10) n (%)	Other (N = 3) n (%)
Stage at initial diagnosis, n (%)				
IB	1 (3.7)	1 (7.1)	0	0
II	4 (14.8)	0	4 (40.0)	0
III	2 (7.4)	2 (14.3)	0	0
IV	18 (66.7)	10 (71.4)	5 (50.0)	3 (100.0)
Missing	2 (7.4)	1 (7.1)	1 (10.0)	0
Time since initial diagnosis, months				
Median	13.50	8.65	21.40	13.50
Range	0.1-114.5	0.1-114.5	1.0-68.9	2.5-40.9
Time since metastatic disease, months				
N	22	10	10	2
Median	8.55	6.70	12.55	22.40
Range	0.1-71.4	0.1-71.4	1.0-68.9	4.3-40.5
Grade, n (%)				
Well differentiated	6 (22.2)	0	6 (60.0)	0
Poorly differentiated	4 (14.8)	2 (14.3)	1 (10.0)	1 (33.3)
Not applicable	4 (14.8)	3 (21.4)	0	1 (33.3)
Unknown	12 (44.4)	8 (57.1)	3 (30.0)	1 (33.3)

Abbreviations: MTC = medullary thyroid cancer; n = number of patients in the specific category; N = number of patients; PTC = papillary thyroid cancer.

Efficacy Results

Table 27.Response Results Based on IRC Assessment RET Fusion-Positive TC Efficacy Analysis Set Study LIBRETTO-121

	Overall Population N = 27		MTC Population N = 14		PTC Population N = 10	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
Objective response rate[a]						
n (%)	12 (44.4)	10 (37.0)	6 (42.9)	5 (35.7)	6 (60.0)	5 (50.0)
95% CI[b]	25.5, 64.7	19.4, 57.6	17.7, 71.1	12.8, 64.9	26.2, 87.8	18.7, 81.3
Best overall response, n (%)						
Complete response (CR)	4 (14.8)	4 (14.8)	1 (7.1)	2 (14.3)	3 (30.0)	2 (20.0)
Partial response (PR)	8 (29.6)	6 (22.2)	5 (35.7)	3 (21.4)	3 (30.0)	3 (30.0)
Stable disease (SD)	8 (29.6)	13 (48.1)	4 (28.6)	8 (57.1)	4 (40.0)	5 (50.0)
SD16+[c]	8 (29.6)	13 (48.1)	4 (28.6)	8 (57.1)	4 (40.0)	5 (50.0)
Progressive disease (PD)	1 (3.7)	2 (7.4)	0	0	0	0
Not evaluable	5 (18.5)	2 (7.4)	3 (21.4)	1 (7.1)	0	0
Clinical benefit rate (CR + uCR[c] +PR + uPR[c] +SD16+[c] weeks[c])[d]						
n (%)	21 (77.8)	23 (85.2)	11 (78.6)	13 (92.9)	10 (100.0)	10 (100.0)
95% CI[b]	57.7, 91.4	66.3, 95.8	49.2, 95.3	66.1, 99.8	69.2, 100.0	69.2, 100.0
Duration of response[f,g]						
Responders, n	12	10	6	5	6	5
Median in months (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Duration of response (n, %)						
< 6 months	0	0	0	0	0	0
≥6 to 12 months	1 (8.3)	1 (10.0)	0	1 (20.0)	1 (16.7)	0
≥12 to 18 months	4 (33.3)	2 (20.0)	2 (33.3)	0	2 (33.3)	2 (40.0)
≥18 to 24 months	2 (16.7)	4 (40.0)	0	3 (60.0)	2 (33.3)	1 (20.0)
≥24 months	5 (41.7)	3 (30.0)	4 (66.7)	1 (20.0)	1 (16.7)	2 (40.0)
Censored n (%)[g]	12 (100.0)	10 (100.0)	6 (100.0)	5 (100.0)	6 (100.0)	5 (100.0)
Reason censored						
Alive without documented disease progression	12 (100.0)	10 (100.0)	6 (100.0)	5 (100.0)	6 (100.0)	5 (100.0)
Rate (%) of duration						

	Overall Population N = 27		MTC Population N = 14		PTC Population N = 10	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
of response[e,f]						
≥6 to 12 months (95% CI)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)
≥12 to 18 months (95% CI)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)
≥24 months (95% CI)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)
Duration of follow-up (months)[e]						
Median	18.69	20.30	25.64	20.37	17.20	18.66
25th, 75th percentile	15.7, 26.0	15.0, 24.9	15.7, 27.9	20.2, 23.3	15.7, 18.7	15.0, 24.9

Abbreviations: CI = confidence interval; CR = complete response; IRC = independent review committee; MTC = medullary thyroid cancer; n = number of patients per category; N = number of patients in population; NE = not evaluable; PD = progressive disease; PR = partial response; PTC = papillary thyroid cancer; RET = Rearranged during Transfection; SD = stable disease; SD16+ = stable disease lasting 16 or more weeks; uCR = unconfirmed CR; uPR = unconfirmed PR.

a 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.

b 95% confidence interval was calculated using Clopper-Pearson method.

c Indicates uPR, uCR, SD lasting ≥16 weeks following initiation of selpercatinib until the criteria for disease progression was first met.

d 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*, uPR*, or SD*. Stable disease was measured from the date for first dose of selpercatinib, until the criteria for disease progression was first met.

e Estimate based on Kaplan-Meier method.

f 95% confidence interval was calculated using Greenwood's formula.

g Status as of the patient's last disease assessment on or before cutoff date.

* Indicates uPR, SD lasting >= 16 weeks following initiation of selpercatinib until the criteria for disease progression was first met.

Progression-Free Survival

Table 28. Progression-Free Survival by Tumor Type Safety Analysis Population Data Cutoff: 13 January 2023

Status	Overall Population N = 27	MTC Population N = 14	PTC Population N = 10
Survival status n (%)			
Died	3 (11.1)	0	0
Censored	24 (88.9)	14 (100.0)	10 (100.0)
Overall survival (months)[a,b]			
Median	NE	NE	NE
95% CI for median	NE, NE	NE, NE	NE, NE
Min, max	0.5, 40.8+	5.0+, 40.8+	4.4+, 30.9+
Duration of follow-up (months)[a]			
Median	21.32	29.95	20.21
25th, 75th percentiles	11.4, 31.2	11.4, 36.1	9.8, 21.7
Rate (%) of overall survival[a,c]			
6 months or more (95% CI)	96.3 (76.5,99.5)	100.0 (NE, NE)	100.0 (NE, NE)
12 months or more (95% CI)	87.7 (66.2,95.9)	100.0 (NE, NE)	100.0 (NE, NE)
24 months or more (95% CI)	87.7(66.2,95.9)	100.0 (NE, NE)	100.0 (NE, NE)

Abbreviations: CI = confidence interval; IRC = independent review committee; max = maximum; min = minimum; MTC = medullary thyroid cancer; n = number of patients in the specific category; N = number of patients; NE = not estimable; PTC = papillary thyroid cancer.

a Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.

b 95% Confidence interval was calculated using Brookmeyer and Crowley method.

c 95% Confidence interval was calculated using Greenwood's formula.

Summary of main studies

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

Table 29. Summary of Efficacy for trial LIBRETTO-001 (LOXO-RET-17001 (J2G-OX-JZJA); Data Cutoff: 13 Jan 2023) - Effects Table for Selpercatinib for the Treatment of Patients with Advanced RET Fusion-Positive Thyroid Cancer

Title: A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumours, Including *RET* Fusion-Positive Solid Tumours, Medullary Thyroid Cancer, and Other Tumours with *RET* Activation (LIBRETTO-001)	
Study identifier	LOXO-RET-17001 (J2G-OX-JZJA)
Design	This is a multicentre, multi-country, open-label, Phase 1/2 study in participants with advanced solid tumours, including REarranged during Transfection (*RET*) fusion-positive solid tumours, *RET*-mutant medullary thyroid cancer, and other tumours with *RET* activation (for example, mutations in other tumour types or other evidence of *RET* activation). This study is ongoing and includes 2 parts: Phase 1 (dose escalation and dose expansion) and Phase 2 (dose expansion). The primary efficacy analysis set includes patients with thyroid cancer who have not been previously treated with systemic therapy other than radioactive iodine.

	Duration of main phase:		The study is ongoing. Patients are to be treated until there is evidence of progressive disease, unacceptable toxicity, or other reason for treatment discontinuation.
Hypothesis	Exploratory: single-arm treatment. For Cohort 2 (patients with *RET* fusion-positive solid tumours without prior standard 1st-line therapy), a true ORR of ≥55% is hypothesised when selpercatinib is administered to such patients		
Treatments groups	Selpercatinib		Phase 2: 160 mg twice daily TC:TrtSysNaïve: n=24
Endpoints and definitions	Primary endpoint	ORR based on IRC assessment	The estimate of ORR will be calculated based on the maximum likelihood estimator (ie, crude proportion of patients with best overall response of CR or PR).
	Secondary endpoint	ORR based on Investigator assessment	The estimate of ORR will be calculated based on the maximum likelihood estimator (ie, crude proportion of patients with best overall response of CR or PR).
	Secondary endpoint	TTR based on IRC and Investigator assessment	TTR is defined as the number of months elapsed between the date of the 1st dose of selpercatinib and the 1st documentation of objective response (CR or PR, whichever occurs earlier) that is subsequently confirmed.
	Secondary endpoint	TTBR based on IRC and Investigator assessment	TTBR is defined as the number of months elapsed between the date of the 1st dose of selpercatinib and the 1st documentation of CR (if patient's best overall response is confirmed CR) or PR (if patient's best overall response is confirmed PR) that is subsequently confirmed.
	Secondary endpoint	DoR based on IRC and Investigator assessment	DoR will be calculated for patients with CR or PR as their best overall response. For such patients, DoR is defined as the number of months from the start date of CR or PR (whichever response status is observed 1st) and subsequently confirmed, to the 1st date that recurrent or disease progression is objectively documented.
	Secondary endpoint	PFS CBR based on IRC and Investigator assessment	PFS is defined as the number of months elapsed between the date of the 1st dose of selpercatinib and the earliest date of documented disease progression or death (whatever the cause).
	Secondary endpoint	OS	OS is defined as the number of months elapsed between the date of the 1st 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.
Database lock	13 January 2023		
Results and Analysis			
Analysis description	Primary Analysis		

Analysis population and time point description	Patients with *RET* fusion-positive TC not previously treated with systemic therapy other than radioactive iodine Efficacy Data Set Data cutoff: 13 January 2023		
Descriptive statistics and estimate variability	Treatment group	Selpercatinib	
		IRC Assessment	Investigator Assessment
	Number of subjects	N=24	N=24
	Number of responders	N=23	N=20
	Objective response rate (95% CI) [a,b]	95.8 (78.9, 99.9)	83.3 (62.6, 95.3)
	Clinical benefit rate (CR + PR + SD-16 weeks) [g] (95% CI) [b]	100.0 (85.8, 100.0)	100.0 (85.8, 100.0)
	Duration of response (months) – Median [c,d] (95% CI)	NE (42.8, NE)	NE (29.7, NE)
	Time to response (months) – Median [e] (25th, 75th percentiles)	1.87 (1.8, 3.6)	1.87 (1.8, 3.6)
	Time to best response (months) – Median [f] (25th, 75th percentiles)	1.87 (1.8, 3.7)	1.87 (1.8, 5.5)
	Progression-free survival (months) – Median [c,d] (95% CI)	NE (44.2, NE)	NE (31.0, NE)
	Overall survival (months) – Median [c,d] (95% CI)	NE (NE, NE)	
	Duration of follow-up (months) – Median (95% CI)	17.81 (9.3, 37.9)	31.74 (7.7, 39.6)

Table 30. 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 (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 (LIBRETTO-121)	
Study identifier	LOXO-RET-18036 (J2G-OX-JZJJ)

<table>
<tr><td>Design</td><td colspan="3">This is a multicentre, open-label, Phase 1/2 study in paediatric and adolescent patients with advanced solid or primary CNS tumours harbouring an activating RET alteration. Selpercatinib is administered as an oral liquid suspension or in capsule form BID, with dose escalation according to evaluations of safety, efficacy, and PK, with a body surface area-based dose in all cohorts.
This study is ongoing and includes 2 parts: Phase 1 (dose escalation and dose expansion) and Phase 2 (dose expansion). The primary objective of the Phase 1 portion of LIBRETTO-121 was to determine the maximum tolerated dose and recommended Phase 2 dose of selpercatinib. The Phase 2 portion will open enrolment when the MTD/ RP2D is confirmed and will enrol patients into one of 4 cohorts. The primary objective of the Phase 2 portion is to determine the ORR based on RECIST 1.1 or RANO as appropriate to tumour type as determined by an IRC.
The disease criteria for each cohort is as follows
• Cohort 1: RET fusion-positive solid tumour (excluding CNS primary) with measurable disease
• Cohort 2: RET-mutant MTC with measurable disease
• Cohort 3: RET fusion-positive primary CNS tumour with measurable disease
• Cohort 4: Any patient with RET mutation/alteration not fitting Cohort 1 to 3 criteria (that is, RET alterations via plasma cfDNA or non-CLIA certified test, measurable, or non-measurable disease).</td></tr>
<tr><td></td><td colspan="2">Duration of main phase:</td><td>The study is ongoing. Patients are to be treated until there is evidence of until progressive disease, unacceptable toxicity, or other reason for treatment discontinuation.</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Exploratory:
For Cohorts 1 and 2, a sample size of 20 patients is estimated to provide approximately 75% power to achieve a lower boundary of a 2-sided 95% exact binomial 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 advancing disease. Cohorts 3-4 are anticipated to enrol too few patients to be powered for a formal statistical testing.</td></tr>
<tr><td>Treatments groups</td><td colspan="2">Selpercatinib</td><td>Phase 2: 92 mg/m^2 BID
Overall Population: n=27</td></tr>
<tr><td></td><td>Primary endpoint (Phase 2)</td><td>ORR based on IRC assessment</td><td>The estimate of ORR will be calculated based on the maximum likelihood estimator (ie, crude proportion of patients with best overall response of CR or PR).</td></tr>
<tr><td></td><td>Secondary endpoint</td><td>ORR and CBR based on IRC and Investigator assessment</td><td>The estimate of ORR will be calculated based on the maximum likelihood estimator (ie, crude proportion of patients with best overall response of CR or PR).</td></tr>
</table>

	Secondary endpoint	DoR based on IRC and Investigator assessment	DoR will be calculated for patients with CR or PR as their best overall response. For such patients, DoR is defined as the number of months from the start date of CR or PR (whichever response status is observed 1st) and subsequently confirmed, to the 1st date that recurrent or disease progression is objectively documented.
	Secondary endpoint	PFS based on IRC and Investigator assessment	PFS is defined as the number of months elapsed between the date of the 1st dose of selpercatinib and the earliest date of documented disease progression or death (whatever the cause).
	Secondary endpoint	OS	OS is defined as the number of months elapsed between the date of the 1st 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.
Database lock	13 January 2023		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Paediatric and adolescent patients with advanced solid or primary CNS tumours harbouring an activating *RET* alteration Efficacy Data Set Data cutoff: 13 January 2023		
Descriptive statistics and estimate variability	Treatment group	Selpercatinib	
		IRC Assessment	Investigator Assessment
	Number of responders, n (%)	12	10
	Objective response rate (95% CI)[a,b]	44.4 (25.5, 64.7)	37.0 (19.4, 57.6)
	Clinical benefit rate (CR + PR + SD-16 weeks) [e] (95% CI) [b]	77.8 (57.7, 91.4)	85.2 (66.3, 95.8)
	Duration of response – Median [c,d] (95% CI)	NE (NE, NE)	NE (NE, NE)
	Progression-free survival (months) – Median [c,d] (95% CI)	NE (NE, NE)	NE (NE, NE)
	Overall survival (months) – Median [c,d] (95% CI)	NE (NE, NE)	

Abbreviations; BID = twice daily; CI = confidence interval; CNS = central nervous system CR = complete response; CBR = clinical benefit rate; DoR = duration of response; IRC = Independent Review Committee; MTC = medullary thyroid cancer; MTD = maximum tolerated dose; N = total number of patients; n = number of patients in specific category; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RANO = Response Assessment in Neuro-Oncology [group]; RECIST = Response Evaluation Criteria in Solid Tumours; RET = REarranged during Transfection; RP2D = recommended Phase 2 dose; SD = stable disease.

[a] ORR is defined as the proportion of patients with BoR of confirmed CR or PR. Response was confirmed by a repeat assessment no less than 28 days.

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

[c] Estimate based on the Kaplan-Meier method.

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

[e] Clinical benefit rate (%) is defined as the proportion of patients with BoR of confirmed CR, PR, or SD lasting 16, or more weeks. Duration of SD was measured from the date of the 1st dose of selpercatinib until the criteria for disease progression were 1st met.

Note: Eligible patients are treated on or before 13 January 2023. SD includes non-CR/non-PD for patients with non-measurable disease.

2.4.1. Paediatric Extrapolation

The justification of the extrapolation of Adult Data to Adolescents provided by the MAH is presented below:

RET is an oncogenic driver, and it is expected that therapeutic benefit of a selective RET inhibitor would be independent of age. For targeted cancer therapies, clinical outcomes for adolescent patients could be extrapolated from clinical trials with predominant enrolment of adult patients as the clinical outcomes are primarily related to the molecular basis of cancer, their associated pathways and PK responses. It is believed that medications designed for some cancers in adults may affect the same pathways in childhood and adolescent cancers (Paulson et al. 2019).

No patients with RET fusion-positive TC aged 18 years or less were identified for participation in LIBRETTO-001. Lilly is using an extrapolation approach from adults to adolescents aged 12 years and above based upon supportive evidence included from the available efficacy and safety data from LIBRETTO-121, and PK data from single-patient compassionate use protocols. A similar pattern of efficacy has been demonstrated with other agents that target oncogenic drivers. Related to this, it is important to note that the RET fusion partners identified in tumours from patients in LIBRETTO-121 were also identified in the tumours seen from LIBRETTO -001. As oncogenic RET fusions seem to be more prevalent in the paediatric DTC patients, treatment with a selective RET inhibitor has been of interest (Paulson et al. 2019). A similar approach was followed for the selpercatinib MTC indication, which has recently been authorised for the indication in adolescent patients aged 12 years and above based on data from 3 adolescent patients in LIBRETTO-001 and from extrapolation of adult data.

To enable an efficacy assessment based on the concept of extrapolation with supportive evidence from the available efficacy and safety analysis from LIBRETTO-121, it is necessary that there is an optimal consideration that the biology of disease, treatment (including targeted treatment), PK exposure, and unmet need are similar for adolescents and adults. The key considerations for justifying the extrapolation of adult data to adolescents aged 12 years and above have been presented as follows:

Pharmacokinetics of selpercatinib in paediatric patients

Evidence from literature shows that adolescents and young adults most commonly demonstrate similar PK responses to adult patients (Bernstein 2011). Based on PK results of paediatric patients treated with selpercatinib in single-patient compassionate use protocols (Section 2.5.3), the PK of selpercatinib in

paediatric patients are similar with the PK results observed in adult patients. No PK data have yet been analysed from LIBRETTO-121.

Need for targeted therapeutic options in paediatric patients

Although the occurrence of TC is rare in children and adolescents, DTC in children and adolescents often follows a more aggressive clinical course when compared with adults. This could be attributed to the disparities observed in the molecular and clinicopathological characteristics observed between adolescent and adult TCs as well as the presence of more advanced disease at the time of diagnosis in children (Paulson et al. 2019).

For adult patients who have RAI-refractory DTC and have exhausted local treatment options, the next step of treatment is with systemic multi-targeted therapies, such as lenvatinib, sorafenib and cabozantinib. However, none of these systemic therapies is approved in paediatric patients less than 18 years of age. There is a need for additional treatment options, especially, targeted treatment agents.

Extrapolation conclusion

In conclusion, based on the observed efficacy and safety in patients aged 12 years and above with RET fusion-positive TC from LIBRETTO-121, the available PK data, mechanism of action of selpercatinib and the high and similar unmet need in both adult and adolescent patients with TC, it is considered that the efficacy and safety data from LIBRETTO-001 in adult patients can be extrapolated to adolescent patients.

2.4.2. Discussion on clinical efficacy

The provided efficacy data in support of the currently intended indication "treatment of adults and adolescents 12 years and older with advanced RET mutant thyroid cancer without prior standard first line therapy (i.e. first-line setting) is based on results from the ongoing study LOXO-RET-17001 (LIBRETTO-001) as of the cut-off date (DCO) of 21 June 2021 which was updated during the procedure with DCO 13 January 2023. This is an open-label, multicentre, phase 1/2 study which consisted of a dose escalation phase (phase 1) to determine the MTD and RP2D of selpercatinib followed by a Phase 2 expansion with diverse RET-altered cancer cohorts (6 cohorts), among them Thyroid Cancer in first line (cohort 2), and other tumours.

The Phase 1 portion of the study has been completed. The Phase 2 portion is ongoing.

Design and conduct of clinical studies

LIBRETTO-001 is non-randomized and non-blinded single arm study. The absence of a control arm is an important limitation and a source of bias for a confirmatory study.

Overall, inclusion and exclusion criteria are considered acceptable.

In agreement with the PIP, Selection criteria allowed to include patients between 12 and 18 years old of age (in 4 countries) but no paediatric patients were enrolled in the study.

The primary endpoint, objective response rate (ORR) based on Independent Review Committee (IRC) assessment using RECIST v1.1, is acceptable. The secondary endpoints (i.e. ORR based on Investigator assessment, TTR, TTBR, DoR, CBR, PFS and OS) are relevant.

Regarding the statistical analysis plan, while a sample size has been well defined for the whole Cohort 2, no minimum recruitment has been defined specifically for the TC subset. This represents a limitation to the interpretation of the results of the study.

Overall, the SAP is acceptable.

Efficacy data and additional analyses

Overall, 921 patients were screened and 796 were enrolled in the pivotal Study LIBRETTO-001. Of these 786, 54 had a *RET* Fusion-Positive Thyroid Cancer (TC). Among them, 46 were included in the Efficacy Analysis Set, 16 patients in the TC:TrtSysNaïve population (without previous systemic treatment) and 30 in the TC:TrtSys (with previous systemic treatment).

Overall, the TC:TrtSysNaïve population remains very limited (i.e. 16) and while it is understood that *RET* Fusion-Positive TC is not common, it is however only the half of the TC:TrtSys population. Data from 8 additional patients with *RET* Fusion-Positive TC without prior systemic treatment have been provided during the assessment with a cut-off date 13 January 2023 bringing the TC:TrtSysNaïve population to 24 patients.

The demographics appears consistent with the condition. The median age was 60.5 years (range: 20 to 84 years), 58.3% of all patients were male. Additionally, the demographics does not present dramatics differences with the TC:TrtSys (with previous systemic treatment) population included in LIBRETTO-001.

The most represented histology TC subtype was papillary TC followed (n=15), and only 1 patient had a poorly differentiated TC which is consistent with the epidemiology of the disease. Patients were in a relatively good condition with 56.3% (n=9) of the patients with an ECOG of 0 and 37.5% (n=6) with an ECOG of 1, and only 1 patient with an ECOG of 2. Additionally, 93.8% (n=15) had a Stage IV disease (IV or IVB or IVC), and 100% (n=16) had a metastatic disease, which is in line with claimed indication (i.e. advance or metastatic cancer). No patients had received previous systemic therapy other than radioactive iodine.

The ORR at the first DCO was 93.8% (95%CI: 69.8, 99.8) as assessed by the IRC and was consistent with the ORR as assessed by Investigators 81.3% (95%CI: 54.4, 96.0). This level of response is seen as promising. Additionally, while the CI interval is broad, the low boundaries remain at a reasonable level of effect. Moreover, these results are consistent with those observed in second line setting (i.e. ORR assessed by IRC: 80.0% (95%CI: 61.4, 92.3).

According to the IRC, at the data cut-off of 21 June 2021, 31.3% (n=5) of the patients had a CR, 62.5% (n=10) a PR, and 6.3% (n=1) SD16+, for a clinical benefit rate of 100% (95%CI: 79.4, 100.0).

At that data cutoff, the data was too immature to provide the estimated median of the DoR, the PFS and the OS. It is nonetheless observed at a median follow-up of 20.1 months (95%CI: 9.3, 25.8), the rate of progression-free survival was 92.9% (95%CI: 59.1, 99.0) and at 24 months was 83.6% (95%CI: 48.0, 95.7).

The TTR and the TTBR assessed by IRC was respectively 1.8 months (25^{th}-75^{th}: 1.8, 4.6), and 3.6 months (25^{th}-75^{th}: 1.8, 5.5).

With the update data, ORR in a total of 24 patients was 95.8% (95%CI: 78.9, 99.9), 20.8 %(n=5) of the patients had a CR, and 75% (n=18) had PR. With a median duration of follow-up of 17.8 months the DoR is not reached.

Overall, the subgroups analysis, including by *RET* fusion partners genes, did not reveal any remarkable difference to main analysis.

Assessment of paediatric data on clinical efficacy

While, for Study LIBRETTO-001 recruitment was open for adolescent (in agreement with the PIP P/0133/2023), no patients with *RET* fusion-positive TC aged 18 years or less were identified for participation in the study. Considering the rarity of the conditions this can be understandable.

In absence of paediatric data in LIBRETTO-001, extrapolation of adult data to adolescents was proposed by the MAH. Extrapolation was justified based on the fact that the therapeutic benefit of a selective RET inhibitor would be independent of age and the clinical outcomes for adolescent patients could be extrapolated from clinical trials with predominant enrolment of adult patients as the clinical outcomes are primarily related to the molecular basis of cancer, their associated pathways and PK responses. Moreover the medications designed for some cancers in adults may affect the same pathways in childhood and adolescent cancers.

These hypotheses were however poorly justified and documented and the arguments provided to justify the extrapolation of the results in adults to the paediatric population were not considered satisfactory.

As of today, there is a lack of age-specific treatment international guidelines. Based on American Thyroid Association (ATA) published paediatric specific treatment guidelines for thyroid cancer (Francis et al. 2015), the primary differences for children and adolescents hinge around prevention of late effects by considering the appropriateness and timing of surgical resection and RAI administration the difference in frequency of molecularly driven thyroid cancers; genomically altered thyroid cancer is predominant in children. This is acknowledged and suggests a similarity in the treatment strategy across the two population. However, this is not a demonstration of the similarity of the disease.

To support an indication in adolescents, data from an ongoing Phase 1/2 paediatric study LIBRETTO-121 were submitted. In this trial overall 31 patients were screened and 27 were enrolled (4 screen failure). Of these, 10 had a *RET* Fusion-Positive TC and were included in the efficacy analysis. Eight patients were aged 12 to 17 years and 2 were aged 18 to 20 years.

ORR was 60.0% (95%CI: 26.2, 87.8) as assessed by the IRC. Three patients had confirmed complete response whilst 3 patients had confirmed partial response. This was consistent with the ORR as assessed by Investigators 50.0% (95%CI: 18.7, 81.3). Although, this level of response can be seen as promising, it appears lower compared to adults. It is acknowledged that 70% of the patients were in 2n+ lines, however the OR remain lower than for adults previously treated with systemic therapy (85.4% (95%CI: 70.8, 94.4)). Three (42.9%) patients with non-measurable disease were included in the study LIBRETTO-121 while none were included in LIBRETTO-001 and patients with non-measurable disease can be considered responders only if they have CR and otherwise must be considered to have non-CR/non-PR or PD. Additionally, paediatric patients with measurable disease (n=4, 57,1%) had an ORR of 100%. Even though uncertainties remained on the effect size, the ORR data in the paediatric population are promising.

Additional efficacy data needed in the context of a conditional MA

The main limitations in relation to the efficacy of selpercatinib are related to the uncontrolled nature of the pivotal evidence which hampers the assessment of the time-to-event endpoints and the limited number of patients included.

To confirm the benefits observed in study LIBRETTO-001 for the adult's patient population and in order to fulfil a CMA the MAH will submit the final data from the cohort 2 of the pivotal study LIBRETTO-001 (Dec 2025).

Data from LIBRETTO-121 are considered immature. In order to confirm the benefits observed in the adolescent patients population 12 year and older and fulfil the CMA criteria, the MAH will submit long-term data from the study LIBRETTO-121 (June 2025).

2.4.3. Conclusions on the clinical efficacy

The efficacy results from the ongoing phase 1/2 study LIBRETTO-001 in patients with systemic treatment naïve RET fusion-positive thyroid cancer and the efficacy result from Phase 1/2 paediatric study, LIBRETTO-121 can be considered clinically meaningful. Although immature, estimates for the secondary endpoint are also promising.

Since efficacy results are still immature, data corresponding to a longer follow-up are required (the SOBs studies related to the CMA).

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- 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 by December 2025
- 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 by June 2025

2.5. Clinical safety

Introduction

Safety data available from a total of 796 patients in the LIBRETTO 001 study which is still ongoing were submitted at the start of the procedure and are presented below. An updated safety data set with a total of 837 patients was submitted and assessed in the context of the annual renewal of Retsevmo (EMEA/H/C/005375/R/0026).

Of the 796 patients, 54 (~ 7%) had RET fusion-positive TC and includes 18 (~34%) who were not previously treated with systemic therapy other than Radioactive iodine (RAI; TC: TrtSysNaïve). All patients in the ITT population received at least one dose of selpercatinib as of the data cut-off date of 15 June 2021.

Table 31. Description of Safety Analysis Sets (data Cut-off: 15 June 2021)

Set Name	Safety Analysis Set	Analysis Set Description	Number of Patients
Overall Safety Population	Overall Safety Analysis Set (OSAS)	All patients who received at least 1 or more doses of selpercatinib regardless of diagnosis or line of therapy.	N = 796
TC Safety Population	TC Safety Analysis Set	All patients with *RET* fusion-positive TC who received at least 1 dose of selpercatinib. This is a subset of the **Overall Safety Population**.	N = 54
TC:TrtSysNaïve (Safety)	**TC:TrtSysNaïve** Safety Analysis Set	All patients with *RET* fusion-positive TC that have had no prior systemic therapy (lenvatinib, sorafenib) and/or other systemic therapy other than RAI, met the criteria in footnote a, and received at least 1 dose of selpercatinib. This is a subset of the **TC Safety Population**.	N = 18
TC:TrtSys (Safety)	**TC:TrtSys** Safety Analysis Set	All patients with *RET* fusion-positive TC previously treated with systemic therapy (lenvatinib, sorafenib), or other systemic therapy, met the criteria in footnote a, and received at least 1 dose of selpercatinib. This is a subset of the **TC Safety Population**.	N = 36

Abbreviations: N = number of subjects in the analysis population; RAI = radioactive iodine; RET = REarranged during Transfection; TC = thyroid cancer; **TC:TrtSys** = Patients Previously Treated with Systemic Therapy in the safety analysis set; **TC:TrtSysNaïve** = Patients Not Previously Treated with Systemic Therapy other than RAI in the safety analysis set.

Patient exposure

Through 15 June 2021, a total of 796 patients have been treated with selpercatinib at doses ranging from 20 mg QD to 240 mg BID, most patients (96%) received at least 1 dose of the selpercatinib recommended dose (Phase 2 dose) of 160 mg BID.

Five hundred thirty-nine (539) patients (68%) were still on study, of which 462 patients (58%, including 39 patients with TC) were still receiving selpercatinib and 77 patients (10%, including 3 patients with TC) were in follow-up, but off treatment. No adolescent patients are present from the ongoing pivotal study LIBRETTO-001 in the advanced RET fusion-positive TC population.

The most common reason for treatment discontinuation in the Overall Safety Population was disease progression (23%), followed by AE (~8%).

The most common reason for treatment discontinuation in the TC Safety Population was disease progression (13%), followed by withdrawal of consent (5.6%), significant non-compliance to protocol (3.7%) and AE (1.9%).

In the TC Safety Population, 94.4% patients received at least 1 dose of selpercatinib 160 mg BID and 94.4% patients had a selpercatinib starting dose of 160 mg.

Table 32. Treatment and study disposition (TC Safety Population)

Status	Treated (N= 36)	Naïve (N= 18)	Total Thyroid (N= 54)
Treatment Status (n, %)			
Discontinued	12 (33.3)	3 (16.7)	15 (27.8)
Continuing	24 (66.7)	15 (83.3)	39 (72.2)
Reason Treatment Discontinued (n, %)			
Progressive Disease	6 (16.7)	1 (5.6)	7 (13.0)
Adverse Event	1 (2.8)	0 (0.0)	1 (1.9)
Requirement for Alternative Treatment per Investigator	1 (2.8)	0 (0.0)	1 (1.9)
Significant Noncompliance to Protocol	2 (5.6)	0 (0.0)	2 (3.7)
Withdrawal of Consent	2 (5.6)	1 (5.6)	3 (5.6)
Other	0 (0.0)	1 (5.6)	1 (1.9)
Study Status (n, %)			
Discontinued	10 (27.8)	2 (11.1)	12 (22.2)
Continuing	26 (72.2)	16 (88.9)	42 (77.8)
Reason Study Discontinued (n, %)			
Withdrawal of Consent	2 (5.6)	1 (5.6)	3 (5.6)
Death	7 (19.4)	1 (5.6)	8 (14.8)
Other	1 (2.8)	0 (0.0)	1 (1.9)

The median time on treatment was 21.3, 20.2 and 22.65 months, respectively, for the Overall Safety Population, overall TC Safety Population and naïve TC population.

The most reported dose modification was dose withheld (72.9% in the Overall Safety Population and 63% in the TC Safety Population) primarily attributed to adverse events (AEs) (64.1% in the Overall Safety Population and 55.6% in the overall TC Safety Population).

Adverse events

A summary of all-causality and treatment-related AEs registered across data-cut-off dates is shown in below table.

Table 33. Treatment-Emergent Adverse Events across Data Cut-Off Dates

	TC:TrtSysNaïve (Safety) Patients	TC Safety Population			Overall Safety Population		
Data cut-off date	15 Jun 2021 N = 18	16 Dec 2019 N = 37	30 Mar 2020 N = 42	15 Jun 2021 N = 54	16 Dec 2019 N = 702	30 Mar 2020 N = 746	15 Jun 2021 N = 796
Any TEAEs, n (%)	18 (100.0)	37 (100.0)	42 (100.0)	54 (100.0)	695 (99.0)	740 (99.2)	795 (99.9)
Related to selpercatinib	18 (100.0)	34 (91.9)	41 (97.6)	53 (98.1)	640 (91.2)	690 (92.5)	756 (95.0)
Grade ≥3 TEAEs, n (%)	10 (55.6)	23 (62.2)	25 (59.5)	37 (68.5)	415 (59.1)	445 (59.7)	572 (71.9)
Related to selpercatinib	8 (44.4)	12 (32.4)	13 (31.0)	17 (31.5)	206 (29.3)	239 (32.0)	307 (38.6)
TESAEs, n (%)	4 (22.2)	13 (35.1)	14 (33.3)	20 (37.0)	234 (33.3)	262 (35.1)	353 (44.3)
Related to selpercatinib	2 (11.1)	1 (2.7)	1 (2.4)	3 (5.6)	54 (7.7)	62 (8.3)	87 (10.9)
TEAEs leading to discontinuation,[a] n (%)	0 (0.0)	2 (5.4)	2 (4.8)	2 (3.7)	37 (5.3)	45 (6.0)	64 (8.0)
Related to selpercatinib	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (2.0)	16 (2.1)	25 (3.1)
Fatal TEAEs, n (%)	0 (0.0)	1 (2.7)	1 (2.4)	1 (1.9)	21 (3.0)	25 (3.4)	45 (5.7)
Related to selpercatinib	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	1 (0.1)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; n = number of patients in specific category; N = number of subjects in the analysis population; RAI = radioactive iodine; TC = thyroid cancer; **TC:TrtSysNaïve (Safety)** = patients not previously treated with systemic therapy other than RAI in the safety analysis set; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

[a] Permanently discontinued.

Table 34. Summary of Treatment-Emergent Adverse overall Safety Population and TC Safety Population

Analysis Set	TC:TrtSysNaïve (Safety) N = 18	TC:TrtSys (Safety) N = 36	TC Safety Population N = 54	Overall Safety Population N = 796
Data cut-off date	**15 Jun 2021**	**15 Jun 2021**	**15 Jun 2021**	**15 Jun 2021**
Any TEAEs, n (%)	18 (100.0)	36 (100.0)	54 (100.0)	795 (99.9)
Related to selpercatinib	18 (100.0)	35 (97.2)	53 (98.1)	756 (95.0)
Grade ≥3 TEAEs, n (%)	10 (55.6)	27 (75.0)	37 (68.5)	572 (71.9)
Related to selpercatinib	8 (44.4)	9 (25.0)	17 (31.5)	307 (38.6)
TESAEs, n (%)	4 (22.2)	16 (44.4)	20 (37.0)	353 (44.3)
Related to selpercatinib	2 (11.1)	1 (2.8)	3 (5.6)	87 (10.9)
TEAEs leading to discontinuation, n (%)	0 (0.0)	2 (5.6)	2 (3.7)	64 (8.0)
Related to selpercatinib	0 (0.0)	0 (0.0)	0 (0.0)	25 (3.1)
Fatal TEAEs, n (%)	0 (0.0)	1 (2.8)	1 (1.9)	45 (5.7)
Related to selpercatinib	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Abbreviations: N = number of patients in the analysis population; n = number of patients in the specific category; TC = thyroid cancer; **TC:TrtSysNaïve (Safety)** = patients not previously treated with systemic therapy other than RAI in the safety analysis set; **TC:TrtSys (Safety)** = patients previously treated with systemic therapy in the safety analysis set; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Table 35. Treatment-Emergent Adverse Events by Decreasing Frequency Any Grade in ≥15% of TC Safety Population Patients Overall Safety Population and TC Safety Population

	TC Safety Population N = 54		Overall Safety Population N = 796	
Preferred or Composite Term	**Any Grade n (%)**	**Grade ≥3 n (%)**	**Any Grade n (%)**	**Grade ≥3 n (%)**
Patients with ≥1 TEAE	54 (100.0)	37 (68.5)	795 (99.9)	572 (71.9)
Oedema	14 (25.9)	0 (0.0)	386 (48.5)	6 (0.8)
Diarrhoea	22 (40.7)	3 (5.6)	370 (46.5)	40 (5.0)
Dry mouth	25 (46.3)	0 (0.0)	344 (43.2)	0 (0.0)
Hypertension	21 (38.9)	9 (16.7)	319 (40.1)	155 (19.5)
Fatigue	25 (46.3)	1 (1.9)	303 (38.1)	18 (2.3)
AST increased	10 (18.5)	3 (5.6)	292 (36.7)	70 (8.8)
ALT increased	11 (20.4)	3 (5.6)	284 (35.7)	91 (11.4)
Constipation	20 (37.0)	0 (0.0)	261 (32.8)	6 (0.8)
Nausea	14 (25.9)	0 (0.0)	248 (31.2)	9 (1.1)
Headache	12 (22.2)	0 (0.0)	219 (27.5)	11 (1.4)
Abdominal pain	17 (31.5)	3 (5.6)	205 (25.8)	20 (2.5)
Blood creatinine increased	10 (18.5)	0 (0.0)	204 (25.6)	6 (0.8)
Vomiting	14 (25.9)	2 (3.7)	178 (22.4)	14 (1.8)
Rash	14 (25.9)	0 (0.0)	173 (21.7)	3 (0.4)
ECG QT prolongation	9 (16.7)	3 (5.6)	165 (20.7)	38 (4.8)
Arthralgia	13 (24.1)	1 (1.9)	165 (20.7)	2 (0.3)
Back pain	13 (24.1)	1 (1.9)	153 (19.2)	12 (1.5)
Cough	10 (18.5)	0 (0.0)	153 (19.2)	0 (0.0)
Decreased appetite	11 (20.4)	0 (0.0)	150 (18.8)	3 (0.4)
Dyspnoea	8 (14.8)	2 (3.7)	150 (18.8)	25 (3.1)
Pyrexia	12 (22.2)	0 (0.0)	135 (17.0)	1 (0.1)
Dry skin	10 (18.5)	0 (0.0)	122 (15.3)	0 (0.0)
Hypocalcaemia	13 (24.1)	1 (1.9)	121 (15.2)	22 (2.8)
Lymphopenia	11 (20.4)	4 (7.4)	111 (13.9)	41 (5.2)

Table 36. Treatment-Emergent Adverse Events Grade ≥3 occurring in ≥2% of Overall Safety Population and TC Safety Population Data Cut-off: 15 June 2021

Preferred or Composite Term	TC Safety Population N = 54 Grade ≥3 n (%)	Overall Safety Population N = 796 Grade ≥3 n (%)
Patients with TEAEs	37 (68.5)	572 (71.9)
Hypertension	9 (16.7)	155 (19.5)
Alanine aminotransferase increased	3 (5.6)	91 (11.4)
Aspartate aminotransferase increased	3 (5.6)	70 (8.8)
Hyponatraemia	4 (7.4)	64 (8.0)
Lymphopenia	4 (7.4)	41 (5.2)
Diarrhoea	3 (5.6)	40 (5.0)
ECG QT prolongation	3 (5.6)	38 (4.8)
Pneumonia	2 (3.7)	34 (4.3)
Dyspnoea	2 (3.7)	25 (3.1)
Thrombocytopenia	2 (3.7)	24 (3.0)
Anaemia	3 (5.6)	23 (2.9)
Hypocalcaemia	1 (1.9)	22 (2.8)
Pleural effusion	1 (1.9)	21 (2.6)
Abdominal pain	3 (5.6)	20 (2.5)
Hypophosphataemia	3 (5.6)	20 (2.5)
Neutropenia	2 (3.7)	20 (2.5)
Fatigue	1 (1.9)	18 (2.3)
Hyperkalaemia	2 (3.7)	16 (2.0)
Sepsis	2 (3.7)	15 (1.9)
Hyperglycaemia	1 (1.9)	13 (1.6)
Back pain	1 (1.9)	12 (1.5)
Embolism	2 (3.7)	6 (0.8)

Abbreviations: ECG = electrocardiogram; N = number of patients; n = number of patients in the specific category; PT = preferred term; TEAE = treatment-emergent adverse event; TC = thyroid cancer.
Notes: The component PTs comprising each composite term are in italics in the Table 8.32.
Adverse events are sorted in descending frequency based on the overall count in the **Overall Safety Population**.
Data cutoff date: 15 June 2021.

The most frequent TEAEs (any grade) occurring in 30% or more in the Overall Safety Population were oedema, diarrhoea, fatigue, dry mouth, hypertension, AST increased, ALT increased, constipation, rash abdominal pain and nausea .

The most frequent TEAEs (any grade) occurring 30% or more in the TC Safety Population were dry mouth, fatigue, diarrhoea, hypertension, constipation, abdominal pain.

The most frequent TEAEs (any grade) occurring 30% or more in the TC: TrtSysNaïve (Safety) were abdominal pain, rash, headache, and lymphopaenia.

The most common Grade ≥3 TEAEs in both the Overall and TC Safety Populations were hypertension followed by ALT increased and AST increased. There were no Grade 5 (fatal) events noted for these 3 TEAEs in either of the populations.

The most frequent Grade 3 or higher TEAEs reported in 5% or more of patients in both the TC: TrtSysNaïve (Safety) patients and Overall Safety Population were hypertension, lymphopaenia hyponatraemia, ALT increased, AST increased, and diarrhoea. There were no Grade 5 (fatal) events noted for these 6 TEAEs in either of the populations.

Serious adverse event/deaths/other significant events

Serious AEs

The most common serious TEAEs observed in both the Overall Safety Population and TC safety population are shown in table below.

Table 37 The most common serious TEAEs observed in both the Overall Safety Population and TC safety population

	TC Safety Population N = 54		Overall Safety Population N = 796	
Preferred Term	**All Causality n (%)**	**Related n (%)**	**All Causality n (%)**	**Related n (%)**
Patients with treatment-emergent SAEs	20 (37.0)	3 (5.6)	353 (44.3)	87 (10.9)
Pneumonia	2 (3.7)	0 (0.0)	33 (4.1)	0 (0.0)
Abdominal pain	3 (5.6)	1 (1.9)	18 (2.3)	3 (0.4)
Dyspnoea	1 (1.9)	0 (0.0)	18 (2.3)	0 (0.0)
Hyponatraemia	1 (1.9)	0 (0.0)	18 (2.3)	0 (0.0)
Diarrhoea	1 (1.9)	0 (0.0)	15 (1.9)	3 (0.4)
Sepsis	2 (3.7)	0 (0.0)	13 (1.6)	0 (0.0)
Alanine aminotransferase increased	1 (1.9)	0 (0.0)	12 (1.5)	9 (1.1)
Aspartate aminotransferase increased	1 (1.9)	0 (0.0)	12 (1.5)	9 (1.1)
Acute respiratory failure	1 (1.9)	0 (0.0)	11 (1.4)	1 (0.1)
Vomiting	2 (3.7)	1 (1.9)	11 (1.4)	1 (0.1)
Pyrexia	2 (3.7)	0 (0.0)	10 (1.3)	2 (0.3)
Dehydration	1 (1.9)	0 (0.0)	9 (1.1)	3 (0.4)

Abbreviations: N = number of patients; n = number of patients in the specific category; SAE = serious adverse event; TC = thyroid cancer.

The most common treatment-emergent serious adverse events (TE-SAEs) occurring in ≥2% of patients in the TC Safety Populations were abdominal pain, pneumonia, sepsis, vomiting and pyrexia.

The most common treatment-emergent serious adverse events (TE-SAEs) occurring in ≥2% of patients in the TC: TrtSysNaïve Population were abdominal pain, sepsis, respiratory failure, vomiting, cardiac failure, diverticulitis, cholestasis, hepatic haemorrhage, and lymphopaenia.

The most common treatment-emergent serious adverse events (TE-SAEs) occurring in ≥2% of patients in both the Overall and TC Safety Populations were pneumonia, abdominal pain.

Deaths

Table 38. Summary of Deaths Overall Safety Population and TC Safety Population

	TC Safety Population N = 54	Overall Safety Population N = 796
Within 28 days of the last dose, n (%)	1 (1.9)	56 (7.0)
Disease progression	1 (1.9)	19 (2.4)
Adverse event	0 (0.0)	34 (4.3)
Other	0 (0.0)	3 (0.4)[a]
More than 28 days after the last dose, n (%)	7 (13.0)	137 (17.2)
Disease progression	5 (9.3)	109 (13.7)
Adverse event	1 (1.9)	10 (1.3)
Other	1 (1.9)[b]	18 (2.3)

Abbreviations: N = number of patients; n = number of patients in the specific category; TC = thyroid cancer.
Note: Percentage is calculated based on the number of patients in the column heading as the denominator.
[a] Other included: disease progression, with additional symptoms, reported as "other".
[b] Other included: (1) bone metastasis.
Data cutoff date: 15 June 2021.

Adverse Events of Special Interest

AST/ALT increased

AST and ALT increases were reported in 36.7% and 35.7% of patients in the Overall Safety Population and 18.5% and 20.4% of patients in the TC Safety Population, respectively. Majority were of Grade 1 or 2.

Hypertension

The incidence of any-grade hypertension was reported in similar proportion in both the Overall Safety Population (41%) and TC safety population (40.7%), 19.7% and 16.7% were Grade ≥3 in the Overall and TC Safety Population, respectively. Patients with a documented history of hypertension displayed a higher incidence of treatment-emergent Grade 3 hypertension than patients without (28% versus 14%, respectively). This trend is the same in the TC safety population (28.6% versus 3.8, respectively).

Hypersensitivity

The overall incidence of any-grade hypersensitivity was 5.9% in the Overall Safety Population. A total of 15 patients (1.9%) in the Overall Safety and none patients in the TC Safety Population had Grade 3 hypersensitivity.

QT prolongation

Electrocardiogram QT prolonged was reported as a TEAE in similar proportion of the patients in both the Overall (21.1%) and TC (16.7%) Safety Populations. Most patients had TEAEs of Grade 1 or 2 in severity in both the Overall Safety (16.3%) and TC safety (11.2%) population.

Laboratory findings

The highest incidence of any grade treatment-emergent laboratory abnormality across haematology parameters was reported for decreased lymphocyte count (51.8% and 57.7%) and decreased white blood cell count (48.7% and 44.2%) in both the Overall Safety Population and the TC Safety Population, respectively.

The highest incidence of any grade treatment-emergent serum abnormality was reported for calcium decreased (58.7 and 59.6 %), and albumin decreased (55.7% and 57.7%) in both the Overall Safety Population and the TC Safety Population, respectively.

Safety in special populations

There were no significant differences in the incidence of TEAEs among the age, sex, and race subgroups in the Overall Safety and TC Safety Populations.

Safety related to drug-drug interactions and other interactions

Please refer to the PK part.

Discontinuation due to adverse events

The most frequently reported TEAEs leading to doses being withheld in 5% or more patients in both the Overall Safety Population and Treatment-Naïve Patients were ALT increase, AST increased and diarrhoea.

The most frequently reported TEAEs leading to a dose reduction in 5% or more patients in both the Overall Safety Population and the TC: TrtSysNaïve Population (safety) were AST increase and diarrhoea.

The most frequently reported TEAEs leading to permanent discontinuation of selpercatinib in 4 or more patients in the Overall Safety Population were ALT increased, fatigue, AST increase, and sepsis. All other AEs occurred in less than 4 patients. In the TC: TrtSysNaïve Population (safety) no events leading to permanent discontinuation of selpercatinib were reported.

Safety in paediatric patient population

The safety data for the paediatric patient population derived from Study LIBRETTO-121. As of 13 January 2023, a total of 8 patients with RET fusion-positive TC aged 12 to 17 years and 2 patients aged 18 to 21 years have enrolled into the Study.

Table 39 shows the overall safety profile and Table *40* shows TEAEs experienced in the 8 adolescent patients with RET fusion-positive TC.

Table 39. Overall Safety RET Fusion-Positive TC Study LIBRETTO-121

Data Cutoff Date	13 January 2023	
	PTC 12 to 21 Years (N = 10)	PTC 12 to 17 Years (N = 8)
N	10	8
n (%)		
Patients with TEAEs	10 (100.0)	8 (100.0)
Patients with TEAEs related to selpercatinib	9 (90.0)	7 (87.5)
Patients with TEAEs Grade 3 or above	4 (40.0)	3 (37.5)
Patients with TEAEs Grade 3 or above and related to selpercatinib	2 (20.0)	2 (25.0)
Patients with permanent discontinuation of selpercatinib due to TEAEs	0 (0.0)	0 (0.0)
Patients with serious TEAEs	0 (0.0)	0 (0.0)

Abbreviations: n = number of patients in the specified category; N = number of patients; PTC = papillary thyroid cancer; RET = REarranged during Transfection; TC = thyroid cancer; TEAE = treatment-emergent adverse events.

Table 40. Treatment-Emergent Adverse Events Experienced by 2 or More Patients by Preferred Term (RET Fusion-Positive Thyroid Cancer Population) Study LIBRETTO-121 Safety Analysis Set

Data Cutoff Date	13 January 2023	
N	PTC 12 to 21 Years (N = 10)	PTC 12 to 17 Years (N = 8)
Preferred Term (n %)		
Diarrhoea	6 (60.0)	4 (50.0)
Corona virus infection	4 (40.0)	4 (50.0)
Oropharyngeal pain	4 (40.0)	4 (50.0)
AST increase	4 (40.0)	4 (50.0)
Cough	4 (40.0)	3 (37.5)
ALT increase	3 (30.0)	3 (37.5)
Blood creatinine increased	3 (30.0)	3 (37.5)
Headache	2 (20.0)	2 (25.0)
Nausea	2 (20.0)	2 (25.0)
Pyrexia	2 (20.0)	2 (25.0)
Abdominal pain	3 (30.0)	2 (25.0)
Blood bilirubin increased	3 (30.0)	2 (25.0)
Fatigue	2 (20.0)	2 (25.0)
Asthenia	2 (20.0)	2 (25.0)
Dizziness	2 (20.0)	2 (25.0)
Neutrophil count decrease	2 (20.0)	2 (25.0)
Dysmenhorrhea	2 (20.0)	2 (25.0)
Eczema	2 (20.0)	1 (12.5)

Abbreviations: AST = aspartate aminotransferase; n = number of patients in the specified category; N = number of patients; PTC = papillary thyroid cancer.

Grade 3 or more TEAEs occurred in 4 patients with RET fusion-positive TC and there

- were 2 events of neutrophil count decrease, Grade 3, assessed as related to selpercatinib by the investigator
- was 1 event of weight gain, Grade 3, assessed as not related to selpercatinib by the investigator
- was 1 event of creatine kinase increase, Grade 4, assessed as not related to selpercatinib by the investigator, and
- was 1 event of epistaxis, Grade 3, assessed as not related to selpercatinib by the investigator.

Post marketing experience

As of April 2022, Selpercatinib was approved in 36 countries including those in the EU, the US and Switzerland for treatment of patients with RET fusion-positive NSCLC and RET-mutant medullary thyroid cancer regardless of line of therapy, and RET fusion-positive TC in the second-line setting. Specific patient populations and dosing guidance vary by country. Cumulatively, up to 30 April 2022, an estimated 1900 patients were exposed to selpercatinib worldwide. The data reported from the post-marketing setting are generally consistent with the known safety profile of selpercatinib. Most events were reported as non-serious, and the most frequently reported events were recognised ADRs for selpercatinib or clinically expected in the target indication.

Overall, no new significant safety information has been identified from post-marketing sources. The periodic safety update report/periodic benefit-risk evaluation report with a data lock of 08 May 2022 confirmed and supported the previously established favourable benefit-risk profile for selpercatinib in the currently approved indications.

2.5.1. Discussion on clinical safety

Whitin this procedure safety was evaluated in patients from the Overall Safety Population (N=796) and in the TC Safety Population (N=54) who received at least 1 dose of selpercatinib as of the data cut-off date of 15 June 2021. The overall Safety Population included in the SmPC (837 patients) derives from Procedure EMEA/H/C/005375/R/0026 concluded on 05/01/2024.

No adolescent patients are present from the ongoing pivotal study LIBRETTO-001 in the advanced RET fusion-positive TC population.

In terms of exposure, the median time on treatment was 21.29 and 20.2 months, respectively, for the Overall Safety Population and TC Safety Population. In the Treatment-Naïve Patients (not previously treated with systemic therapy other than RAI - TC: TrtSysNaïve patients) (n=18), the median treatment duration is 22.3 months (range: 0.4 to 35.6 months) and 86.2% of patients were on treatment for at least 24 months.

The median relative dose intensity was similar for the Overall Safety Population (94.5%) and the TC Safety Population (96.9%).

The most reported dose modification was dose withheld (72.9% in the Overall Safety Population and 63.0% in the TC Safety Population) primarily attributed to adverse events (AEs) (64.2% in the Overall Safety Population and 57.4% in the TC Safety Population).

The types and incidence rates of AEs leading to doses being withheld, dose reductions, and treatment discontinuation were consistent between the Overall Safety Population and Treatment-Naïve Patients (not previously treated with systemic therapy other than RAI - TC:TrtSysNaïve patients).

The most frequent TEAEs reported in 2% or more patients both in the Overall Safety Population and TC: TrtSysNaïve (Safety) were pneumonia and abdominal pain.

Fatal TEAEs were reported in 21 patients at the initial MAA compared with 45 patients at the 15 June 2021 data cut-off. In Treatment-Naïve Patients, a fatal (Grade 5) TEAE was experienced by one patient late onset and due to disease progression.

The adverse events of special interest (AESIs) analysed did not change compared to those reported previously for Retsevmo.

The safety profile observed in the data from the 15 June 2021 cut-off and from the 13 January 2023 cut-off (procedure EMEA/H/C/005375/R/0026 concluded on 05/01/2024) concluded on 05.01.2024). remains consistent with previously reported data. No new ADRs or AESIs have been identified since initial authorisation and the safety profile is consistent between the TC: TrtSysNaïve patients and the Overall Safety Population.

There were 8 patients < 18 years (range 12-17) of age with RET fusion positive thyroid cancer in LIBRETTO 121. No unique safety findings in children aged less than 18 years have been identified.

The safety profile of the existing key risks of liver injury and cardiac arrhythmia due to QT prolongation were consistent with the previous analysis.

Additional safety data needed in the context of a conditional MA

Although safety results remain consistent with previously reported data they come from a low number of adult and paediatric patients with TC:TrtSysNaïve. Further safety data will be provided from LIBRETTO-001 and study LIBRETTO-121 as specific obligations (SOBs).

2.5.2. Conclusions on clinical safety

The overall safety profile of selpercatinib in the Patients with Thyroid Carcinomas Not Previously Treated with systemic therapy other than RAI is overall consistent with that of the Overall Safety Population. The safety data submitted as part of this application indicate a safety profile for selpercatinib consistent with that reported previously.. Longer-term safety data from adult and paediatric patient with TC:TrtSysNaïve will be provided from LIBRETTO-001 and study LIBRETTO-121 as specific obligations (SOBs).

2.5.3. 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 5.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.3 with the following content:

Safety concerns

Table 41. List of Safety Concerns

List of Safety Concerns	
Important identified risks	None
Important potential risks	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

The existing list of safety concerns remain unchanged,

Pharmacovigilance plan

Routine pharmacovigilance activities remained sufficient to characterise the risks of the product in all approved indications.

Risk minimisation measures

Table 42. Part V.2.- Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

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 and Breastfeeding follow-up forms **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 pharmacokinetics 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.

Routine risk minimisation measures remain sufficient to mitigate the risks of selpercatinib in all indications.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2,4,4, 4.8 and 5.1, 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 proposed revisions do not significantly affect the overall readability. It is not considered necessary to conduct consultation with target patient groups further to that performed for the initial MAA.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication is:

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)

3.1.2. Available therapies and unmet medical need

Standard options for patients in first-line with advanced thyroid cancer refractory to iodine include sorafenib and levantinib according to ESMO guidelines. However, no targeted agents are approved as first-line therapy for patients with *RET* fusion-positive thyroid cancer.

3.1.3. Main clinical studies

Clinical efficacy and safety of selpercatinib in treatment of (i) adults with an advanced *RET* fusion-positive thyroid cancer without prior standard first line therapy, and (ii) adolescents with an advanced *RET* fusion-positive thyroid cancer (i.e. first and second line) are based on analyses of the interim data from LIBRETTO-001 (LOXO-RET-17001) and LIBRETTO-121 respectively.

LIBRETTO-001 is a global, multi-cohort, open-label, phase 1/2 study in adult and adolescent patients with advanced RET-altered tumours. The phase 2 portion evaluates efficacy in cohorts based on tumour type, type of RET alteration, and prior treatment. The primary objective was to determine ORR by IRC assessment according to RECIST 1.1. DOR, PFS and OS were secondary endpoints.

LIBRETTO-121 is a multicenter, open-label, Phase 1/2 study in pediatric patients (≥ 12 years of age and ≤ 21 years) with an advanced solid or primary CNS tumor harboring an activating *RET* alteration (LIBRETTO-121.

3.2. Favourable effects

Of the *RET* fusion-positive thyroid cancer patients naive to systemic therapy other than radioactive iodine, and enrolled in LIBRETTO-001, 24 patients had the opportunity to be followed for at least 6 months and were considered efficacy eligible.

At the data cut-off of 13 January 2023, 8 more patients were included in the analysis. The data showed an ORR in a total of 24 patients of 95.8% (95%CI: 78.9, 99.9), with 20.8 %(n=5) of the patients with CR, and 75% (n=18) with PR. With a median duration of follow-up of 17.8 months, the DoR was not reached (95% CI: 42.8 months, not estimable).

As of 13 January 2023, 10 patients with *RET* fusion-positive thyroid cancer aged 12 to ≤ 21 years have been treated in LIBRETTO-121. Of these 10 patients, 8 patients were less than 18 years of age. Of the 10 patients, 4 were previously treated with radioactive iodine only, 2 had received prior systemic therapy that did not include radioactive iodine and 4 were not previously treated with any systemic therapy. For all 10 patients, objective response rate was 60.0% (95% CI: 26.2, 87.8) per IRC. Three (3) patients had confirmed complete response whilst 3 patients had confirmed partial response.

3.3. Uncertainties and limitations about favourable effects

The uncertainties and limitations are mainly related to the uncontrolled nature of the pivotal trial which hampers the interpretation of the time-to-event endpoints (PFS, OS).

Contextualisation of the data coming from an uncontrolled study with the results of other systemic therapy (e.g. lenvatinib and sorafenib) is challenging given that response rates observed for selpercatinib have been reported in a selected patient population including only patients with RET fusions, while other medicines have been investigated in unselected patient populations.

The selected population raises several concerns: progressive disease status at baseline was not a selection criteria, status of having received RAI prior selpercatinib at inclusion was not recorded in a clear manner, and there is a lack of information on screening failure.

The efficacy data are yet mature and longer follow-up is needed.

These remaining limitations will be addressed post authorisation with the submission of updated data and longer follow-up from the studies LIBRETTO-001 and LIBRETTO-121 (SOBs).

3.4. Unfavourable effects

Safety data assessed in the current procedure are available from a total of 796 patients the LIBRETTO-001 study. The safety data from 837 patients reflected in the SmPC were assessed in procedure EMEA/H/C/005375/R/0026 concluded on 05/01/2024.

Safety was evaluated in patients in the Overall Safety Population (N=796) and in the TC Safety Population (N=54) who received at least 1 dose of selpercatinib as of the data cut-off date of 15 June 2021.

In terms of exposure, the median time on treatment was 21.29 and 20.2 months, respectively, for the Overall Safety Population and TC Safety Population. In the Treatment-Naïve Patients (not previously treated with systemic therapy other than RAI - TC: TrtSysNaïve patients) (n=18), the median treatment duration is 22.3 months (range: 0.4 to 35.6 months) and 86.2% of patients were on treatment for at least 24 months.

The most frequent TEAEs (any grade) occurring 30% or more in the TC: TrtSysNaïve (Safety) were abdominal pain, rash, headache, and lymphopaenia.

The most frequent Grade 3 or higher TEAEs reported in 5% or more of patients in both the TC: TrtSysNaïve (Safety) patients and Overall Safety Population were hypertension, lymphopaenia hyponatraemia, ALT increased, AST increased, and diarrhoea.

The most common treatment-emergent serious adverse events (TE-SAEs) occurring in ≥2% of patients in the TC Safety Populations were abdominal pain, pneumonia, sepsis, vomiting and pyrexia.

The most common treatment-emergent serious adverse events (TE-SAEs) occurring in ≥2% of patients in the TC: TrtSysNaïve Population were abdominal pain, sepsis, respiratory failure, vomiting, cardiac failure, diverticulitis, cholestasis, hepatic haemorrhage, and lymphopaenia.

In TC: TrtSysNaïve Population, there was 1 death in total that occurred more than 28 days after the final dose of selpercatinib due to disease progression. No patients experienced a fatal (Grade 5) TEAE.

The adverse events of special interest (AESIs) analysed did not change compared to those reported previously.

3.5. Uncertainties and limitations about unfavourable effects

No adolescent patients are present from the ongoing pivotal study LIBRETTO-001 in the advanced RET fusion-positive TC population and data from study LIBRETTO-121 are limited to 10 paedatric patients. Data in adults are limited to 24 patients. Data on long-term safety in adult and adolescent will be provided from LIBRETTO-001 and study LIBRETTO-121 as specific obligations (SOBs).

3.6. Effects Table

Table 37. Effects Table for selpercatinib for the Treatment adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer in the first-line setting (data cut-off: 15 June 2021 and 13 January 2023)

Effect		Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects							
Treatament of TCTrtSysNaïve (n=24) Cut-off date 13 Jan 2023							
ORR	Rate		% (95% CI)	95.8 (78.9, 99.9)	NA	- Absence of comparative data -	LIBRETTO-001
DoR	Median		Months (95% CI)	NE (42.8, NE)	NA		
Cut-off date 15 June 2021							
TTR	Median		Months (25^{th}, 75^{th} perc.)	1.8 (1.8, 4.6)	NA		
TTBR	Median		Months (25^{th}, 75^{th} perc.)	3.6 (1.7-13.8)	NA		
PFS	Median		Months (95% CI)	NE (19.3, NE)	NA		
OS	Median		Months	NE	NA		

Effect		Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			(95% CI)	(NE, NE)			
Unfavourable Effects TCTrtSysNaïve (n=24)							
AEs grade ≥3	Adverse events grade 3-4 regardless causality		%	55.6%	*NA*	Uncontrolled data	
AEs grade ≥3	Serious AEs regardless causality		%	22.2%	*NA*		
Deaths	Number of deaths		Absolute value (%)	% (n=0)	*NA*		
QT prolongation	AE of special interest		%	22.2%	*NA*		
AST increased	AE of special interest		%	11.1%	*NA*		
ALT increased	AE of special interest		%	16.7%	*NA*		

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

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Data supporting this application for selpercatinib as monotherapy for adults with advanced *RET* fusion-positive thyroid cancer without prior standard first line therapy (i.e. first-line setting), is based on a single-arm study LIBRETTO-001, which remains largely exploratory and make interpretation of time to event endpoints and any potential long-term benefit challenging.

Nevertheless, this approach is acceptable in the context of a CMA for a product intended for a patient population with high unmet medical need when the observed ORR is outstanding and durable.

The obtained ORR of 95.8 % is considered meaningful in patients with RET- fusion-positive TC in first-line setting.

Median DOR was not reached at a median follow-up time of 17.8 months and rate of patients with duration response at 12 and 24 months suggest lasting benefits from treatment with selpercantinib.

Other approved front-line therapies with established benefit are approved, and an indirect comparison could not be performed due to the specificity of selpercatinib molecular target. The activity of selpercatinib is however considered compelling.

The safety profile observed in the data from the 15 June 2021 cut-off and data from 13 June 2023 cut-off submitted in the context of the parallel procedure EMEA/H/C/005375/R/0026 remains consistent with previously reported data. No new ADRs or AESIs have been identified since initial authorisation and the safety profile is consistent between the Treatment-Naïve Patients and the Overall Safety Population.

To support the extension of indication in adolescent 12 years of age and older with advanced *RET* fusion-positive thyroid cancer data from study LIBRETTO-121 have been provided. Even though the efficacy results from LIBRETTO-121 were lower than anticipated with an ORR of 60.0% (95% CI: 26.2, 87.8), the ORR remains positive and promising. Additional Efficacy and Safety Data from LIBRETTO--001 and LIBRETTO-121 Studies will be provided to address remaining uncertainties.

3.7.2. Balance of benefits and risks

The provided results from LIBRETTO-001 and LIBRETTO-121 have shown activity in term of tumour shrinkage. Responses appear durable and the safety profile is consistent with that reported previously.

In view of the remaining uncertainties related to the limited data set and duration of follow-up, final efficacy and safety data are required as confirmatory evidence (SOBs).

3.7.3. Additional considerations on the benefit-risk balance

As comprehensive data on the product are not available in the first-line treatment of RET- fusion-positive TC, a conditional marketing authorisation was requested by the applicant for this extension of indication. The new indication for this product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed above.
- It is likely that the applicant will be able to provide comprehensive data. The applicant will provide final efficacy and safety data with longer follow-up for both the adults and paediatric patient populations. Results are expected with LIBRETTO-001 study, Cohort 2 by December 2025 for the adult population and with LIBRETTO-121 study by June 2025 for the paediatric population.
- Unmet medical need will be addressed. One factor preventing inter-study comparison with other MKIs is the difference between patient populations. Indeed, response observed in selpercatinib have been observed in a population including only patients with RET fusions, while other approved medicines in TC have been investigated in an unselected patient population. The missing information is relative sensitivity of patients with tumours harbouring RET fusion to MKIs (lenvatinib and sorafenib) when compared to unselected patients. The MKI with the higher estimated ORR is lenvatinib with 65% (95% CI: 59.0; 71.0). Considering that the ORR of selpercatinib in this selected patient population is outstanding with 95.8% (95% CI: 78.9, 99.9), it is unlikely that the RET TC naïve patients treated with Lenvatinib or sorafenib would experience a dramatically higher response rate compared to the unselected patients. Altogether, it is considered that a major therapeutic advantage over the existing authorised medicinal products in the overlapping indication is demonstrated.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Given the positive benefit/risk and the unmet medical need in the applied indication as described above, this is considered fulfilled.

3.8. Conclusions

The overall B/R of Retsevmo for the first line 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) is positive subject to the specific obligations and conditions imposed in order to inform the long-term efficacy and safety profile of the product in this new indication.

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 - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, and IIIB

Extension of indication to include the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer in the first-line setting for RETSEVMO based on interim data from studies LIBRETTO-001 (LOXO-RET-17001) and LIBRETTO-121; LIBRETTO-001 is an open-label, multicentre, global Phase 1/2 study of selpercatinib in patients with RET-altered advanced solid tumors. LIBRETTO-121 is a Phase 1/2 study of selpercatinib in paediatric patients with advanced RET-altered solid or primary central nervous system tumours. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.3 of the RMP has been agreed.

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.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Retsevmo is not similar to Sorafenib within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

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.

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

Risk management plan (RMP)

The Marketing authorisation holder (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.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

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
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