EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2022
EMA/681951/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP group of variations including an extension of indication assessment report

Invented name: Retsevmo

International non-proprietary name: selpercatinib

Procedure No. EMEA/H/C/005375/II/0014/G

Marketing authorisation holder (MAH) Eli Lilly Nederland B.V.

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 events of special interest

ADR adverse drug reaction

ALT alanine aminotransferase

AST aspartate aminotransferase

AUC24 area under the concentration versus time curve, from time 24 hours

BID twice daily

Cab cabozantinib

CBR clinical benefit rate

CHMP Committee for Medicinal Products for Human Use

CI confidence interval

Cmax maximum observed drug concentration

CR complete response

CSR clinical study report

DOR duration of response

ECG electrocardiogram

IRC independent review committee

MAA marketing authorisation application

MTC medullary thyroid cancer

MKIs multikinase inhibitors

NMD non-measurable disease

NSCLC non-small cell lung cancer

ORR objective response rate

OS overall survival

PD Progressive disease

PFS progression-free survival

PR partial response

PT preferred term

QD Once daily

QTc corrected QT interval

RECIST Response Evaluation Criteria in Solid Tumors

RET REarranged during Transfection

SAE serious adverse event

SmPC Summary of Product Characteristics

SMQ standardised MedDRA query

TEAE treatment-emergent adverse event

TLS tumour lysis syndrome

Trt treatment

ULN upper limit of normal

Van vandetanib

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 1 April 2022 an application for a group of variations.

The following variations were requested in the group:

Variations requested		Type	Annexes affected
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	Type IB	None
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 first-line treatment of advanced RET-mutant medullary thyroid cancer (MTC) in adults and adolescents 12 years and older based on interim results from Study LIBRETTO-001 (LOXO-RET-17001) on the clinical safety and efficacy of selpercatinib in patients with RET-mutant MTC who are cabozantinib and vandetanib treatment-naïve (MTC:-Cab/-Van). LIBRETTO-001 is a global, multicohort, open-label, Phase 1/2 study in adult and adolescent patients with advanced RET-altered tumours. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflelt is updated in accordance. Version 2.1 of the RMP has also been submitted.
As part of the application the MAH is requesting a 1-year extension of the market protection.
The application also includes an updated Phase II Environmental Risk Assessment in order to reflect the patient population as per the approved indication.

The group of variations 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 P/0398/2021on the granting of a (product-specific) waiver and on the granting of a class waiver.

At the time of submission of the application, the P/0398/2021was not yet completed as some measures were deferred.

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC)

726/2004 - one year of market protection for a new indication.

Scientific advice

The Applicant received Protocol Assistance on the development relevant for the approved indication from the CHMP, on 25 July 2019 (EMEA/H/SA/4170/1/2019/PA/III). The advice pertained to the following clinical aspects of the dossier:

- The design of a Phase 1/2 study LOXO-RET-17001, and particularly:
  - Regarding the RET-mutant MTC cohort, the adequacy of the proposed population, and the inclusion of a TKi-naïve subgroup to support a benefit/risk assessment in independent of line of therapy.
  - The adequacy of the proposed datasets to support a benefit/risk assessment in RET-mutant MTC.
- The design of a proposed randomized, open-label, Phase 3 study J2G-MC-JZJB in TKi-naïve patients with locally advanced or metastatic MTC, in particular the proposed patient population, the choice of comparator, the primary endpoint, the possible crossover to the active treatment arm, the statistical plan, and the approach to collection of patient-reported outcomes.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	1 April 2022
Start of procedure:	23 April 2022
CHMP Rapporteur Assessment Report	23 June 2022
PRAC Rapporteur Assessment Report	24 June 2022
PRAC members comments	29 June 2022
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	07 July 2022
CHMP members comments	11 July 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 July 2022
Opinion	21 July 2022
The CHMP adopted a report on similarity of Cometriq with name of the authorised orphan medicinal product(s) on date (Appendix 1)	21 July 2022
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Retsevmo in comparison with existing therapies (Appendix 2)	21 July 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The MAH is seeking an extension of indication of selpercatinib for the first line treatment of advanced RET-mutant medullary thyroid cancer (MTC).

Selpercatinib has a conditional approval for previously treated advanced RET mutant MTC (cabozantinib and/or vandetanib).

Epidemiology and risk factors, screening tools/prevention

Thyroid cancer can be broken down into 4 main types: papillary, follicular, medullary and anaplastic. Of these 4, medullary thyroid cancer (MTC) is a rare subtype representing about 3% to 5% of all thyroid cancers (Accardo et al. 2017). Medullary thyroid cancer is an uncommon malignant tumour arising from the calcitonin- producing parafollicular cells (C cells) of the thyroid. Robust epidemiology data specific to MTC are sparse.

In adults, MTC occurs as a sporadic entity in 70% to 80% of cases and as familial MTC in 25% of cases. In paediatrics, the aetiology is reversed, with most cases familial in nature and the minority of cases being sporadic. RET point mutations, insertions, or deletions are present in most MTCs, including both familial (i.e., multiple endocrine neoplasia [MEN] and other familial MTC syndromes) and sporadic cases (Ji et al. 2015; Heilmann et al. 2016). An estimated 65% to 90% of sporadic MTCs contain RET mutations (Moura et al. 2009; Romei et al. 2018; Larouche et al. 2019).

Biologic features

RET is a receptor tyrosine kinase critical to development of the enteric nervous system and kidneys. Genetic alterations in RET have been implicated in the pathogenesis of several human cancers including NSCLC, poorly differentiated thyroid cancers, and MTCs. RET can become oncogenically activated through two primary mechanisms:

1- chromosomal rearrangements, which produce cytoplasmically localised oncogenic hybrid proteins that fuse the RET kinase domain with a partner protein dimerisation domain and lead to ligand-independent constitutive activity,

and

2- point mutations, insertions, and deletions (indels), which directly or indirectly activate the kinase.

RET point mutations, insertions, or deletions are present in most MTCs (Ji et al. 2015; Heilmann et al. 2016).

Clinical presentation, diagnosis and stage/prognosis

Although the overall 10-year survival rate for patients with MTC is high (75% to 85%), the clinical course of MTC is highly heterogeneous, varying from indolent tumours that remain unchanged for many years to aggressive cancers associated with high mortality. However, survival decreases with locally invasive and locally advanced disease. Although surgery can be curative for approximately 85% of patients who present with localized disease, recurrence develops in up to 50% of all patients after surgery (Wells et al. 2015). Metastatic MTC is considered incurable and MTC patients with distant metastasis have a 5-year survival of 38% after initial diagnosis (American Cancer Society [https://www.cancer.org/cancer/thryoid-cancer/detectiondiagnosis- staging/survival-rates]). Distant metastasis is the main cause of death in MTC patients. Oncogenic RET mutations occur in the majority of MTCs (Ji et al. 2015), including more than 90% of hereditary MTCs and 50% to 60% sporadic MTC (Donis- Keller et al. 1993; Mulligan et al. 1993; Eng et al. 1994; Hofstra et al. 1994; Agrawal et al. 2013; Ji et al. 2015).

Management

MTC is not sensitive to radioactive iodine and is only curable through surgical resection (Pacini et al. 2012), but recurrent disease occurs in approximately 50% of patients after resection (Wells et al. 2015). Locally recurrent disease is treated with reoperation and/or external beam radiation therapy. However, these treatments are associated with significant morbidity and are often not curative. Metastatic MTC is managed with resection, radiation, or systemic therapies as noted below, but is currently incurable. Children and adolescents with MTC are treated in the same manner as adults, with initial thyroidectomy then re-resection, radiation, or systemic therapy with recurrent disease (Starenki and Park 2015).

There are no RET-specific inhibitors licensed for the treatment of first-line RET-mutant MTC. The unselective MKIs vandetanib and cabozantinib are approved for the treatment of patients with unresectable locally advanced or metastatic MTCs, in adults and including children over the age of 5 in the case of vandetanib, irrespective of the RET status and irrespective of prior treatment. Cabozantinib and vandetanib have shown tumour response rates in MTC of 28% and 45% and PFS improvements (over placebo) of 7.2 and 11.2 months, respectively; neither drug has demonstrated an OS benefit (Elisei et al. 2013; Wells et al. 2015).

Patients with advanced RET-mutant MTC have a poor prognosis and a significant unmet medical need.

2.1.2. About the product

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

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

1) the treatment of metastatic RET fusion-positive NSCLC in adult patients who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy,

2) RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib and

3) RET-mutant MTC in adult and pediatric patients 12 years of age and older who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

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 (NSCLC and non-medullary thyroid cancer) or mutation (MTC) 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.

On 21 June 2022, an extension of indication of selpercatinib for the first line treatment of metastatic RET fusion-positive NSCLC Not previously treated with a RET inhibitor was granted.

The MAH is seeking an extension of indication of selpercatinib for the first line treatment of advanced RET mutant MTC

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

Selpercatinib is currently being investigated in the Phase 1/2 study, LIBRETTO-001 (LOXO-RET-17001). It is a multicenter, single-arm, multicohort, open-label, dose-escalation study in patients 12 years or older with advanced solid tumours, including RET fusion-positive solid tumours, RET-mutant MTC, and other tumours with RET activation.

LIBRETTO-001 was initiated in May 2017. The Phase 1 portion of the study has been completed, and the Phase 2 portion is ongoing.

CHMP protocol assistance was sought on the design of LIBRETTO-001 to support an indication in RET-mutant MTC, including whether the inclusion of a small number of patients (at least 10) without prior vandetanib/cabozantinib therapy could support an initial MAA for a broader indication including TKi-naïve patients. CHMP considered that ORR data from such a small number of patients would likely not be sufficient to establish a benefit-risk in first line patients.

Data at the DCO date of 15 June 2021 are submitted to support the use of selpercatinib for the treatment of RET mutant advanced MTC regardless of line of therapy. The exploratory objectives are not presented at the DCO.

2.1.4. General comments on compliance with GCP

The MAH stated that the clinical trial LOXO-RET-17001 that support the proposed indication of selpercatinib was conducted in accordance with 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, and the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guideline (E6).

The clinical trial LOXO-RET-17001 (LIBRETTO-001) conducted outside the European Union meets the ethical requirements of Directive 2001/20/EC.

Study LOXO-RET-17001 was subject to independent audit by regulatory authorities. The audits performed as of 15 June 2021 were:

Agency Name	Audit Dates	Audit Site
US FDA	8 Jan 2020 to 14 Jan 2020	University of Texas MD Anderson Cancer Center
US FDA	27 Jan 2020 to 7 Feb 2020	The Ohio State University
US FDA	30 Jan 2020 to 10 Feb 2020	Massachusetts General Hospital
Pharmaceuticals and Medical Devices Agency of Japan	17 May 2021 to 17 May 2021	Japan Affiliate

Abbreviations: US FDA = United States Food and Drug Administration

2.2. Non-clinical aspects

2.2.1. Introduction

The specific inhibitory activity of selpercatinib against RET-dependent tumours has been demonstrated in several in vitro and in vivo studies. Single and repeat dose pharmacokinetic studies have characterized the ADME profile in animals. Repeated-dose toxicity studies of up to 3 months duration were conducted in rats and minipigs. Toxicities common to both species and specific to each were observed and reported in the SmPC. The genotoxicity study revealed an equivocal result in the in vivo micronucleus test. The toxicity study program is satisfactory under ICH S9.

2.2.2. Ecotoxicity/environmental risk assessment

Selpercatinib is an inhibitor of the RET tyrosine kinase (encoded by the RET proto-oncogene).

It is used to treat some cancers caused by abnormal changes in the RET gene, which have spread and/or which cannot be removed by surgery:

- non-small cell lung cancer, in adults,

- thyroid cancer in adults,

- medullary thyroid cancer, in adults and adolescents from 12 years of age.

The prevalence calculations are admissible and comply with guidance document EMEA/CHMP/4447/00. The predicted environmental concentration PECsw of selpercatinib in surface water is at 0.033 µg/L, therefore higher than the limit value (0.01 µg/L) set by the guide document EMEA/CHMP/4447/00. Additional phase II trials were therefore conducted.

Regarding phase II studies :

Part A: Fate in the environment

The adsorption coefficient Koc was established on 4 soils and 3 sludges from treatment plants (OECD 106). Adsorption is particularly strong on soils (320285 L/kg on average) whereas it is 988 L/kg on average on sludge.

The high adsorption properties of selpercatinib are also noted in the aquatic sediment degradation study (OECD 308) in which selpercatinib rapidly partitioned into the sediment layer with a half-life in water of less than 'one day. The hydrolysis of selpercatinib (OECD 111) shows that the product is not very hydrolysable with a half-life greater than 1 year regardless of the pH. Aerobic transformation in a sludge system is evaluated according to the OECD 314B protocol. Selpercatinib undergoes multiple transformations with a product representing more than 10% of the initial radioactivity. The time of disappearance of 50% of the product (DT50) is 3.46 days in the test and, after adjusting the temperatures, it is established at 7.4 days.

The aerobic transformation in an aquatic sedimentary system is evaluated according to the OECD 308 protocol. The time of disappearance of 50% of the product (DT50) is, after temperature adjustment, 257 and 338 days depending on the sediment tested. Consequently, a test on sedimentary organisms (chironomids) was carried out in Phase II Tier B.

Tier A: Effects on aquatic organisms

A respiration inhibition test on activated sludge was performed according to the OECD 209 protocol. The no observed effect concentration (NOEC) for activated sludge microorganisms is 1000 mg/L. An algae growth inhibition test was performed according to the OECD 201 protocol. The no observed effect concentration (NOEC) for algae is 1700 µg/L. A reproduction test on Daphnia magna daphnia was carried out according to the OECD 211 protocol.

The NOEC for daphnids is 97 µg/L for mortality, reproduction and growth. A test on Pimephales promelas fish was carried out according to the OECD 210 protocol. The NOEC for fish is 160 µg/L. A test on sedimentary organisms (chironomids) was carried out according to the OECD 218 protocol. The NOEC for chironomids is 298 mg/kg. Based on these ecotoxicity test results, the predicted PNEC no-effect concentrations for the different organisms are established. The PEC/PNEC ratios were calculated and are all well below 1. Selpercatinib therefore does not appear to present a risk to aquatic organisms in the environment.

Tier B

The bioconcentration factor in BCF fish was measured (OECD 305) since the log Kow of selpercatinib is greater than 3 at pH 7 and pH 9. The normalized values of BCF being 98 and 42 L/kg, they are lower than the threshold of 2000 L/kg. Selpercatinib therefore does not meet the criterion for bioaccumulation.

PBT potential

The OECD 308 sediment transformation test shows that selpercatinib is very persistent in sediments and fulfills the vP criterion. However, it does not meet the vB criterion since the OECD fish bioaccumulation test showed that the BCF bioconcentration factor is below the regulatory classification thresholds. It is neither bioaccumulable (BCF<2000 L/kg), nor very bioaccumulable (BCF<5000 L/kg). Selpercatinib is therefore not classified as vPvB.

Summary of main study results

Substance (INN/Invented Name): selpercatinib/Retsevmo			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH 5 = 1.30 pH 7 = 3.08 pH 9 = 3.45	Not B
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	pH 5 = 1.30 pH 7 = 3.08 pH 9 = 3.45	not B
	BCF	BCFKgL = 98 and 42 L·kg-1	not B
Persistence	DT50 or ready biodegradability	Sediment (two systems): - DT50 water: 1.6, 0.8 d	vP

		- DT50 sediment: 336, 418 d - DT50 whole system: 257, 338 d			
Toxicity	NOEC or CMR	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 class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	*Soil:* *Koc = 116050 L·kg-1 (soil 1)* *Koc = 341959 L·kg-1 (soil 2)* *Koc = 582830 L·kg-1 (soil 3)* *Koc = 240301 L·kg-1 (soil 4)* *Sludge:* *Koc = 683 L·kg-1 (sludge 1)* *Koc = 1180 L·kg-1 (sludge 2)* *Koc = 1102 L·kg-1 (sludge 3)*			Soil: average Koc used in ERA, 320285 L·kg-1
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308 DT50 at 12°C	System 1 at 12°C - DT50, water = 1.6 days - DT50, sediment = 336 days - DT50, whole system = 257 days - shifting to sediment = 97.6% System 2 at 12°C - DT50, water = 0.8 days - DT50, sediment = 418 days - DT50, whole system = 338 days - shifting to sediment = 99.4%			Two water, sediment systems evaluated. Sediment risk assessment triggered
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	1700 1700	μg/L	Growth rate Yield
Daphnia sp. Reproduction Test	OECD 211	NOEC	97	μg/L	Production of immobile offspring
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	160	μg/L	Total length, wet weight, dry weight
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	⩾ 1000 000	μg/L	Total respiration
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	1987	mg/kg	Chironomus riparius

2.2.3. Discussion and conclusion on non-clinical aspects

The ERA for Retsevmo (selpercatinib) file is complete and generally well constructed. It does not give rise to any particular comments and the MAH's conclusions are acceptable. Selpercatinib does not appear to pose a risk to aquatic organisms in the environment and is not classified as a PBT or vPvB. The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of selpercatinib.

The MAH is however recommended to amend the calculations and information regarding the study on aerobic transformation in aquatic sediment systems according to OECD 308 as follows:

i) The MAH should use the SFO kinetic instead of DFOP for the DT50 derivation of total system 1, Brandywine creek.

ii) The MAH should correct the study summaries in the ERA and in the study report in terms of the kinetic used to derive the DT50 value for total system 2, Choptank River.

iii) The MAH should recalculate the DT50 values for the water compartments using the FOMC kinetic.

iv) The MAH should provide a table in the ERA summarising all DT50 values at 20 and 12 °C.

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 Number	**Study Title**
LOXO-RET-17001	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)

2.3.2. Pharmacokinetics

The pharmacokinetic (PK) properties of selpercatinib were sufficiently characterized in the initial MAA.

There are neither new PK data that would change the main PK features of selpercatinib nor special populations. Also, no revision of section 5.2 PK properties of the SmpC is claimed.

The PK data provided in support of this submission include:

- Descriptive, noncompartmental methods of analysis of selpercatinib PK data from all MTC patients enrolled in the pivotal study **LOXO-RET-17001** (LIBRETTO-001) as of the submission data cut-off date (10 June 2021) and, The PK data of MTC patients from the pivotal study **LOXO-RET-17001** are presented in the paragraph "PK in target population". For DDI data, Please refer to the paragraph "Pharmacokinetic interactions studies".

Pharmacokinetic in target population

PK data from study **LOXO-RET-17001** as of the data cutoff of 10 June 2021 were previously reported in the NSCLC CSR (please refer to EMEA/H/C/005375/II/0011). Of the 757 patients with evaluable PK data, 313 were MTC patients.

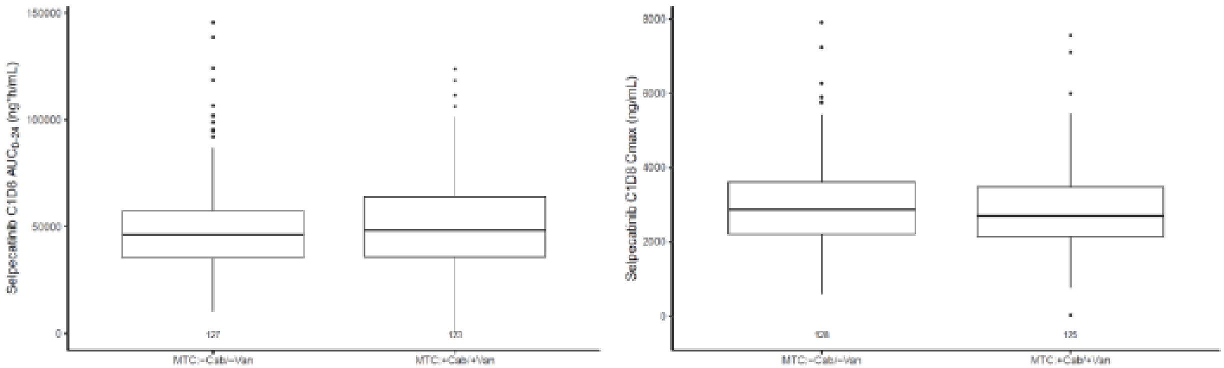
Table 1 presents the available steady-state exposure (AUC0-24 and Cmax at steady state [C1D8]) of selpercatinib for patients with MTC taking 160 mg selpercatinib BID with (MTC: +Cab/+Van) or without (MTC:-Cab/-Van; naïve patients) a previous treatment by cabozantinib and/or vandetanib. Figure 1 presented the associated box-plots to visualize the PK parameters distribution.

Table 1: Steady-state (C1D8) PK parameters of selpercatinib in patients with MTC

	MTC:-Cab/-Van		MTC:+Cab/+Van	
	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)
N	128	127	125	123
GM	2830	46700	2630	45500
GCV%	42	46	64	66
95% CI	1130, 5880	18400, 117000	929, 5940	16600, 106000

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours; CI = confidence interval; C_{max} = maximum plasma concentration; GCV% = geometric coefficient of variation %; GM = geometric mean; MTC = medullary thyroid cancer; N = number of samples.
Sources: Data available from 09 May 2017 to 10 June 2021.

Figure 1: Boxplots of plasma selpercatinib Cmax and AUC0-24 following selpercatinib 160 mg BID administrations (C1D8)



The steady-state exposure for selpercatinib in MTC: -Cab/-Van patients and MTC: +Cab/+Van patients was comparable. The geometric mean AUC0-24and Cmax PK parameters were similar and the 95%CI overlapped substantially in MTC: -Cab/-Van and MTC: +Cab/+Van patients.

2.3.3. Pharmacodynamics

Mechanism of action

Selpercatinib is an inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase. Certain point mutations in RET or chromosomal rearrangements involving in frame fusions of RET with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers by promoting cell proliferation of tumour cell lines. In in vitro and in vivo tumour models, selpercatinib demonstrated anti-tumour activity in cells harboring constitutive activation of RET protein resulting from gene fusions and mutations, including CCDC6 RET, KIF5B RET, RET V804M, and RET M918T. In addition, selpercatinib showed anti-tumour activity in mice intracranially implanted with a patient-derived RET fusion-positive tumour.

Primary and secondary pharmacology

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

2.3.4. PK/PD modelling

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

2.3.5. Discussion on clinical pharmacology

In the current submission, PK data in MTC patients from the pivotal study LOXO-RET-17001 (cut-off date of 10 June 2021, N=313) were provided. Using a NCA approach, PK exposure parameters at steady-state (AUC0-24h, Cmax) were determined from MTC patients RET-naïve (max n=128) and RET-prior (max n=125). Overall*,* steady state systemic exposure of selpercatinib in patients with MTC naïve vs those with prior systemic therapy appears to be similar.

2.3.6. Conclusions on clinical pharmacology

Overall, no significant difference in PKs characteristics of selpercatinib is observed in patients with MTC RET-naïve (-Cab/-Van) compared to patients with MTC RET-prior systemic therapy (+Cab/+Van).

2.4. Clinical efficacy

2.4.1. Dose response study

Study LIBRETTO-001 is an open-label, multicentre, global Phase 1/2 study of selpercatinib in patients with RET-altered advanced solid tumours that was initiated in May 2017. The Phase 1 portion of the study allowed to determine the maximum tolerated dose and recommended Phase 2 dose of selpercatinib. A dose of 160 mg BID was selected for Phase 2.

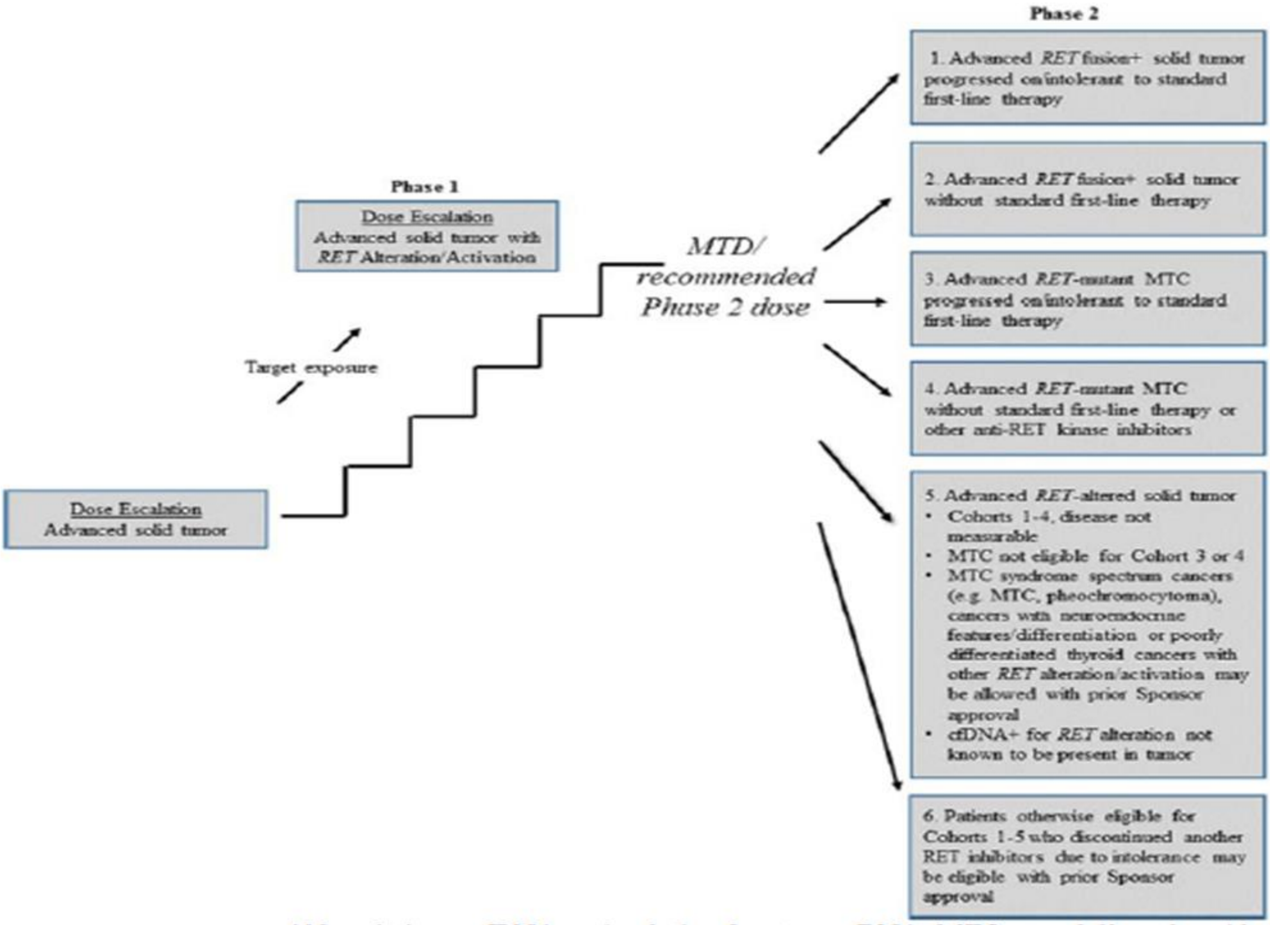
The approved dose as recommended in the SmPC is 160 mg taken orally twice daily (body weight 50 mg or greater).

2.4.2. Main study

Study LOXO-RET-17001 (LIBRETTO-001): A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumours, Including RET 0Fusion-Positive Solid Tumours, RET-mutant Medullary Thyroid Cancer (MTC), and Other Tumours with RET Activation

Methods

Figure 2: depicts the study design for the latest protocol version 9.0.



Abbreviations: cfDNA = circulating free tumor DNA; MTC = medullary thyroid cancer; MTD = maximum tolerated dose.

Study participants

Eligibility criteria remained mostly the same as specified in the previous CSR (17 June 2019 data cutoff, see EPAR for Retsevmo initial MA), except for the following listed below, which were updated in version 8.0 or 9.0 of the protocol.

Inclusion Criteria for Phase 1

- Inclusion Criterion [2] – amended to remove the prohibition of prior treatment with a selective RET inhibitor(s) (including investigational selective RET inhibitor[s]).
- Inclusion Criterion [5] - amended to note the exclusion of minor patients in Canada and Germany.

- Criterion [11]: - allowed enrolment of patients with adequate renal function, with estimated glomerular filtration rate ≥ 30 mL/minute (up to 6 participants with an eGFR ≥ 15 and < 30 mL/minute were allowed to enroll with Sponsor approval).
- Criterion [13]: - amended to include additional details on observing conventional and effective birth control for the duration of treatment and for 3 months

<u>Inclusion Criteria for Phase 2</u>

- Inclusion Criterion [1] – updated standard of care therapy criteria for Cohorts 2 and 4.
- Inclusion Criterion [5] - added to describe the inclusion criteria for Cohort 6: Participants who were otherwise eligible for Cohorts 1 to 5 who discontinued another RET inhibitor due to intolerance could be eligible with prior Sponsor approval.

<u>Exclusion Criteria for Phase 1 and Phase 2:</u>

- Exclusion Criterion [2] - amended to further describe the inclusion criteria for Cohorts 1 through 6.
- Exclusion Criterion [3] - modified to further describe exclusion criteria for investigational agents or anticancer therapies.
- Exclusion Criterion [8] - modified to revise the criterion for QTcF.
- Exclusion Criterion [9] - amended to exclude patients with serious ongoing intercurrent illness, such as hypertension or diabetes, despite optimal treatment.
- Exclusion Criterion [13] – amended to further clarify prohibited concomitant medications.
- Exclusion Criterion [17] - added to exclude patients with a history of hypersensitivity to any of the study intervention capsule components.

Treatments

The RP2D of selpercatinib (160 mg BID) was selected in Phase 1 and has been used as the starting dose for patients in the Phase 2 dose expansion phase of the study.

Patients continued selpercatinib dosing in 28-day cycles until PD, unacceptable toxicity, or other reason for treatment discontinuation. Patients with PD could continue selpercatinib if, in the opinion of the Investigator, the patient was deriving clinical benefit from continuing study treatment, and continuation of treatment was approved by the Sponsor.

Objectives and endpoints

Table 2. Objectives and endpoints of LIBRETTO-001 (Phase 2)

Objectives (Phase 2)	Endpoints (Phase 2)
Primary	
• To assess the antitumor activity of selpercatinib in patients with *RET*-mutant MTC	• ORR based on IRC assessment using RECIST 1.1
Secondary	
• To assess the antitumor activity of selpercatinib in patients with *RET*-mutant MTC	• ORR based on Investigator assessment using RECIST 1.1 • TTR, TTBR, DoR, CBR based on IRC and Investigator assessment • PFS based on IRC and Investigator assessment • OS
• To determine the safety profile and tolerability of selpercatinib in patients with *RET*-mutant MTC	• 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 • ECGs
• To characterize 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; MTC = medullary thyroid cancer; 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; TEAE = treatment-emergent adverse event; T_{max} = time to maximum plasma concentration; TTBR = time to best response; TTR = time to response.

Sample size

Under the planned primary analysis of effectiveness, a true ORR of ≥ 40% is hypothesized when LOXO-292 is administered to patients with RET-mutant MTC who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options.

A sample size of 55 patients is estimated to provide 89% power to achieve a lower boundary of a 2-sided 95% exact binomial confidence interval (CI) about the estimated ORR that exceeds 20%. Ruling out a lower limit of 20% for ORR is considered clinically meaningful patients who have failed prior multikinase inhibitor therapy (eg, cabozantinib and/or vandetanib), are in need of systemic therapy, and have limited treatment options for their advancing disease. Under the primary analysis, the lower limit of the 95% CI will exceed 20% when the estimated ORR is 33% or greater (Clopper-Pearson method).

Randomisation

The study was not randomised.

Blinding (masking)

The study was not blinded.

Statistical methods

Statistical Analysis Plan

The protocol (appendix [Protocol and Addenda]) and the SAPs approved prior to database lock (appendix [Documentation of Statistical Methods]) provide the planned analyses for the study, comparisons, statistical tests, and determination of sample size.

This interim report provides clarification regarding the derivation of the analysis sets that support evaluation of the MTC data for selpercatinib.

Analysis Sets

Patients enrolled into the Phase 1 dose escalation as well as the Phase 1 and Phase 2 dose expansion cohorts were grouped to derive the analysis sets.

The goal of the arrangement of these various data sets was to:

-maximize information through the consolidation of data from both Phase 1 and Phase 2 parts of LIBRETTO-001, and

-define groupings based on clinically meaningful distinctions, resulting in similarity of patients within a group, thus, facilitating the interpretation of results.

Efficacy Analysis Set for RET-Mutant MTC

Patients with RET-mutant MTC 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 is assessed approximately every 2 months, and 6 months of follow up provides sufficient time for initial responses to be confirmed.

The evaluation of efficacy consists of RET-mutant MTC analysis sets as defined in Table 3.1 (the basis for the initial regulatory submissions) and includes patients enrolled into Phase 2 Cohorts 3, 4, and 5. Cohort 6 includes patients who have received prior treatment with a selective RET inhibitor but discontinued due to intolerance and are therefore not included in the efficacy analysis; these patients were excluded in LIBRETTO-001 until Cohort 6 was introduced in protocol version 8.

The efficacy analysis for RET-mutant MTC primarily focused on 1) patients not previously treated with cabozantinib and vandetanib (primary efficacy analysis set) and 2) patients previously treated with cabozantinib and/or vandetanib (supportive efficacy analysis set). A total of 314 RET-mutant MTC patients were considered part of the efficacy evaluable dataset. Efficacy was further assessed using the supportive efficacy analysis sets described in Table 3.

Table 3: Description of Efficacy Analysis Sets

Set Name	Analysis Set	Analysis Set Description	Number of Patients Per Analysis Set (Total MTC Efficacy Evaluable Dataset N 314)
Primary Efficacy Analysis Set			
MTC:-Cab/-Van Previously labelled as *"Supplemental Analysis Set 1 (SAS1)"*	Patients Not Previously Treated with Cabozantinib and/or Vandetanib	Includes *RET*-mutant MTC patients that have had no prior systemic therapy or have been treated with a prior systemic therapy besides cabozantinib and vandetanib; and met the criteria in footnote a.	N=142 *Includes N=115 from* ***MTC:TrtNaive*** *and N=27 from* ***MTC:TrtOther***
Supportive Efficacy Analysis Set			
MTC:+Cab/+Van Previously labelled as *"Integrated Safety Analysis Set (IAS)"*	Patients Previously Treated with Cabozantinib and/or Vandetanib	Includes all patients with *RET*-mutant MTC previously treated with cabozantinib and/or vandetanib; and met the criteria in footnote a.	N=151 *Includes N=55 from* ***MTC:Initial+Cab/+Van***
Other Supportive Efficacy Analysis Sets (available in Section 8)			
MTC:Initial+Cab/+Van Previously labelled as *"Primary Analysis Set (PAS)"*	The First 55 Patients Enrolled who were Previously Treated with Cabozantinib and/or Vandetanib	This analysis set is a subset of the "Patients Previously Treated with Cabozantinib and/or Vandetanib" analysis set. Includes the first 55 consecutively enrolled patients with *RET*-mutant MTC previously treated with cabozantinib and/or vandetanib; and met the criteria in footnote a.	N=55
MTC:NMD Previously labelled as *"Supplemental Analysis Set 2 (SAS2)"*	Patients with Non-Measurable Disease	Includes patients with *RET*-mutant MTC previously treated and treatment naïve patients without measurable disease by RECIST v1.1; and met criteria 1 and 3 in footnote a.	N=21
MTC:TrtNaive	Patients Naïve to Any Systemic Therapy	This analysis set is a subset of the "Patients Not Previously Treated with Cabozantinib and/or Vandetanib" analysis set.	N=115
MTC:TrtOther	Patients Naïve to Cabozantinib and Vandetanib But Previously Treated with Other Systemic Therapy	This analysis set is a subset of the "Patients Not Previously Treated with Cabozantinib and/or Vandetanib" analysis set.	N=27

Abbreviations: CLIA = Clinical Laboratory Improvement Amendments; MTC = medullary thyroid cancer; **MTC:-Cab/-Van** = Patients Not Previously Treated with Cabozantinib and/or Vandetanib; **MTC:+Cab/+Van** = Patients Previously Treated with Cabozantinib and/or Vandetanib; **MTC:Initial+Cab/+Van** = The First 55 Patients Enrolled who were Previously Treated with Cabozantinib and/or Vandetanib; **MTC:NMD** = Patients with Non-Measurable Disease; **MTC:TrtNaive** = Patients Naïve to Any Systemic Therapy; **MTC:TrtOther** = Patients Naïve to Cabozantinib and Vandetanib But Previously Treated with Other Systemic Therapy; N = number of patients; RECIST = Response Evaluation Criteria in Solid Tumors; RET = REarranged during Transfection; SAP = statistical analysis plan; SCE = Summary of Clinical Efficacy.

a Criteria for inclusion:

1. Evidence of a protocol-defined qualifying and definitive *RET* mutation 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 MTC SCE SAP for details.
3. Received 1 or more doses of selpercatinib.

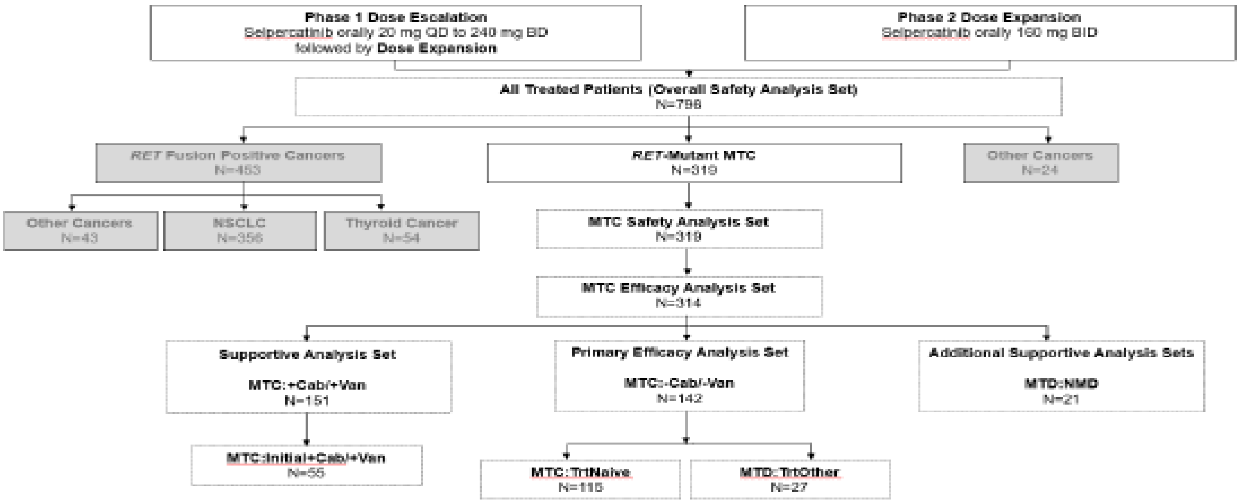
The efficacy analysis sets were derived to facilitate the regulatory review of the LIBRETTO-001 data. These analysis sets are distinctive from those specified in the protocol and documented in the SAP. This interim CSR follows the SAP (appendix [Documentation of Statistical Methods]) prepared to document and specify the statistical methods used for analyses to demonstrate the effectiveness and the safety of selpercatinib in patients with RET-mutant MTC.

There were no changes in the planned analyses for the study.

Results

Participant flow

Figure 3: RET-mutant MTC efficacy analysis and overall safety populations based on a data cutoff date of 15 June 2021.



Abbreviations: BID = twice daily; MTC = medullary thyroid cancer; **MTC:-Cab/-Van** = Patients Not Previously Treated with Cabozantinib and/or Vandetanib; **MTC:+Cab/+Van** = Patients Previously Treated with Cabozantinib and/or Vandetanib; **MTC:Initial+Cab/+Van** = The First 55 Patients Enrolled who were Previously Treated with Cabozantinib and/or Vandetanib; **MTC:NMD** = Patients with Non-Measurable Disease; **MTC:TrtNaïve** = Patients Naïve to Any Systemic Therapy; **MTC:TrtOther** = Patients Naïve to Cabozantinib and Vandetanib But Previously Treated with Other Systemic Therapy; MTD = maximum tolerated dose; nonmeasurable disease; N = number of patients; NMD = nonmeasurable disease; NSCLC = non-small-cell lung cancer; QD = once daily; RET = REarranged during Transfection.

Table 4: Summary of Disposition RET-Mutant MTC Efficacy Analysis Population Data Cutoff: 15 June 2021

n (%)	Primary Analysis Set MTC:-Cab/-Van N=142	Subsets of Primary Analysis Set MTC:TrtNaive N=115	Subsets of Primary Analysis Set MTC:TrtOther N=27	Supportive Analysis Set MTC:+Cab/+Van N=151	Total MTC[a] N=314
Treatment continuing	118 (83.1)	96 (83.5)	22 (81.5)	86 (57.0)	221 (70.4)
Treatment discontinued	24 (16.9)	19 (16.5)	5 (18.5)	65 (43.0)	93 (29.6)
Progressive disease	5 (3.5)	2 (1.7)	3 (11.1)	35 (23.2)	40 (12.7)
Adverse event	8 (5.6)	7 (6.1)	1 (3.7)	12 (7.9)	21 (6.7)
Intercurrent illness compromising ability to fulfil protocol requirements	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.3)
Requirement for alternative treatment per investigator	1 (0.7)	1 (0.9)	0 (0.0)	2 (1.3)	4 (1.3)
Withdrawal of consent	6 (4.2)	6 (5.2)	0 (0.0)	3 (2.0)	10 (3.2)
Death	2 (1.4)	1 (0.9)	1 (3.7)	6 (4.0)	8 (2.5)
Other	2 (1.4)	2 (1.7)	0 (0.0)	6 (4.0)	9 (2.9)
Treatment post-progression	15 (10.6)	10 (8.7)	5 (18.5)	47 (31.1)	62 (19.7)
Study status continuing	128 (90.1)	103 (89.6)	25 (92.6)	99 (65.6)	246 (78.3)
Study status discontinued	14 (9.9)	12 (10.4)	2 (7.4)	52 (34.4)	68 (21.7)
Withdrawal of consent	6 (4.2)	6 (5.2)	0 (0.0)	9 (6.0)	16 (5.1)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.3)
Death	8 (5.6)	6 (5.2)	2 (7.4)	39 (25.8)	47 (15.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.0)	4 (1.3)

Abbreviations: MTC = medullary thyroid cancer; **MTC:+Cab/+Van** = Patients Previously Treated with Cabozantinib and/or Vandetanib; **MTC:NMD** = Patients with Non-Measurable Disease; **MTC:TrtNaïve** = Patients Naïve to Any Systemic Therapy; **MTC:TrtOther** = Patients Naïve to Cabozantinib and Vandetanib But Previously Treated with Other Systemic Therapy; N – number of patients; n = number of patients in specific category; NMD = nonmeasurable disease; RET = REarranged during Transfection.

a The total column is calculated from the presented **MTC:-Cab/-Van** (N=142) plus **MTC:+Cab/+Van** (N=151) as well as the **MTC:NMD** (N=21) Analysis Sets.

Recruitment

This study was conducted at 80 centres that enrolled patients in North America, Asia Pacific, European Union, and the Middle East. The study is ongoing.

Study initiation date: 09 May 2017

Data cutoff date for interim analysis: 15 June 2021

Participants screened: 921

Participants treated with at least 1 dose of selpercatinib: 796

Participants with RET mutant MTC: 319

Conduct of the study

The protocols located in the previous CSR (15 June 2021 data cutoff) provide information about changes in study conduct implemented up to protocol version 9.0. The protocol located in an appendix to this CSR provides information about changes in study conduct implemented by protocol version 9.0 (03 June 2020).

Table 5: Summary of major changes, subsequent amendments, and the approval dates of the protocol.

Version Number and Date	Major Changes to the Protocol
8.0 10 June 2019	• New sections were added to define length of study and end of study • The LTFU plan was updated to occur approximately every 3 months until the participant has withdrawn consent, is lost to follow-up, has died, or the sponsor makes a decision to close the study. • Phase 2 descriptions were updated to increase participant numbers following the selection of 160 mg BID as the RP2D and to account for addition of a new cohort (Cohort 6). • Eligibility criteria were added, removed, or modified (as detailed in protocol Section 3.3.1). • Additional details were provided regarding the study intervention (protocol Section 3.4.1). • Additional Investigator guidance regarding possible AEs and re-escalations were provided. • Tests and evaluations were updated to add tests at additional time points and increase frequency of tests (as described in Section 7 of the protocol [appendix Protocol and addenda]). • Sample size was updated to reflect updated size for Cohort 1 and Cohort 6. • Statistical portions were updated to align with other protocol sections. • Clarification that efficacy analyses will be conducted on the Safety Analysis Set unless otherwise specified (as described in protocol Section 3.7). • Definition of life-threatening AEs was updated. Examples of multiple kinase inhibitors and RET activating mutations were updated.
8.1 (Denmark) 10 June 2019	Major changes from protocol version 7.3 (Denmark) to version 8.1 were: • Rationale for enrolling participants younger than 18 years was provided to indicate that participants younger than 18 years could be enrolled if approved by local institutional and country regulatory authorities. • All other revisions were made to align with version 8.0.
8.2 (Japan) 14 June 2019	Major changes from protocol version 7.2 (Japan) to version 8.2 were: • Study design was updated to add clarification of enrollment in Japan. • All other revisions were made to align with version 8.0.
8.3 (Germany) 08 October 2019	Major changes from protocol version 7.4 (Germany) to version 8.3 were: • Clinical safety and data updates were made to align with IB version 5.0. • Size of Cohort 1 was increased to up to approximately 200 participants. • Cohort 6 was added for participants who discontinued another RET inhibitor due to intolerance (up to approximately 50 participants). • The 40 mg capsule and liquid suspension were added; the 10 mg capsule was removed. • The ECG schedule was updated.
Addendum 1 to V8.0-8.3 02 April 2020	The purpose of this addendum was to allow temporary flexibility in study visits, assessments, and study drug dispensation because of the COVID-19 pandemic. The information in this addendum supplements Protocol Section 7 and Table 7-1 in Protocol version 8.0, version 8.1, version 8.2, and version 8.3.
9.0 (Global) 03 June 2020	Major changes from protocol version 8.3 (Germany) to version 9.0 were: • Aligned changes added in response to EC/RA queries in PA8.1 (Denmark), PA8.3 (Germany), and PA8 addendum (Canada). • Clinical safety and data updates were made to align with the IB V7.0. • Size of Cohort 1 was increased to approximately 250 participants and Cohort 5 up to approximately 200. • Reduced the requirement for in-clinic visits beyond C7 and provided the options of telemedicine and visits to local healthcare providers during nondisease assessment cycles.

Abbreviations: AE = adverse event; BID = twice daily; C = cycle; COVID-19 = coronavirus disease 2019; EC = Ethics Committee; ECG = electrocardiogram; IB = Investigator's Brochure; LTFU = long-term follow-up; RA =

Protocol Deviations

Important protocol deviations were defined as those which could potentially impact the study assessment, participant rights, and the study integrity. Protocol deviations were reviewed by the Sponsor and none of these deviations were considered to have a marked impact on safety or efficacy evaluations.

Important protocol deviations for this interim analysis were the same as those reported in the previous NSCLC CSR (15 June 2021 data cutoff).

Table 6: Summary of Important Protocol Deviations Data Cutoff: 15 June 2021

Category	NSCLC Safety Population (N=356) n (%)	Overall Safety Population (N=796) n (%)
Patients with Major Protocol Deviations	92 (25.8)	161 (20.2)
Investigational Product	33 (9.3)	61 (7.7)
Study Procedures	21 (5.9)	43 (5.4)
SAE Reporting	18 (5.1)	35 (4.4)
Restricted Concomitant Medication Change	19 (5.3)	23 (2.9)
Inclusion Criteria	12 (3.4)	16 (2.0)
Withdrawal Criteria	7 (2.0)	11 (1.4)
Exclusion Criteria	3 (0.8)	5 (0.6)
Informed Consent	2 (0.6)	4 (0.5)

Abbreviations: N = number of patients; n = number of patients in specific category; NSCLC = non-small cell lung cancer; SAE = serious adverse events.

Source: Table 8.6.

Baseline data

Demographics

Table 7: Summary of Demographics RET-Mutant MTC Efficacy Analysis Population Data Cutoff: 15 June 2021

Parameter	Primary Analysis Set MTC:-Cab/-Van N=142	Subsets of Primary Analysis Set MTC:TrtNaive N=115	Subsets of Primary Analysis Set MTC:TrtOther N=27	Supportive Analysis Set MTC:+Cab/+Van N=151	Total MTC[a] N=314
Age (years, n)					
Median (Range)	57 (15-87)	57 (15-87)	58 (21-77)	58.0 (17-90)	58 (15-90)
Overall age group, n (%)					
<18 years	2 (1.4)	2 (1.7)	0 (0.0)	1 (0.7)	3 (1.0)
18-44 years	34 (23.9)	27 (23.5)	7 (25.9)	29 (19.2)	69 (22.0)
45-64 years	68 (47.9)	54 (47.0)	14 (51.9)	68 (45.0)	145 (46.2)
65-74 years	23 (16.2)	20 (17.4)	3 (11.1)	37 (24.5)	64 (20.4)
75-84 years	14 (9.9)	11 (9.6)	3 (11.1)	14 (9.3)	30 (9.6)
≥85 years	1 (0.7)	1 (0.9)	0 (0.0)	2 (1.3)	3 (1.0)
Sex, n (%)					
Male	83 (58.5)	71 (61.7)	12 (44.4)	96 (63.6)	190 (60.5)
Female	59 (41.5)	44 (38.3)	15 (55.6)	55 (36.4)	124 (39.5)
Race, n (%)					
White	123 (86.6)	99 (86.1)	24 (88.9)	136 (90.1)	277 (88.2)
Black or African American	2 (1.4)	2 (1.7)	0 (0.0)	2 (1.3)	4 (1.3)
Asian	8 (5.6)	6 (5.2)	2 (7.4)	2 (1.3)	13 (4.1)
Native Hawaiian or Other Pacific Islander	1 (0.7)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.3)
Other	7 (4.9)	7 (6.1)	0 (0.0)	10 (6.6)	17 (5.4)
Missing	1 (0.7)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.3)
Ethnicity, n (%)					
Hispanic or Latino	7 (4.9)	6 (5.2)	1 (3.7)	10 (6.6)	18 (5.7)
Not Hispanic or Latino	132 (93.0)	108 (93.9)	24 (88.9)	137 (90.7)	289 (92.0)
Missing	3 (2.1)	1 (0.9)	2 (7.4)	4 (2.6)	7 (2.2)
Body weight (kg)					
n	142	115	27	151	314
Median	73.2	74.1	65.2	67.6	71.1
Range	26.8-179.4	26.8-148.3	41.9-179.4	36.5-176.8	26.8-179.4
Baseline ECOG performance status, n (%)					
0	69 (48.6)	53 (46.1)	16 (59.3)	41 (27.2)	120 (38.2)
1	67 (47.2)	58 (50.4)	9 (33.3)	99 (65.6)	177 (56.4)
2	6 (4.2)	4 (3.5)	2 (7.4)	11 (7.3)	17 (5.4)
Calcitonin (pg/mL)					
n	142	115	27	150	313
Median	5198.5	3793.0	7548.0	5758.5	5135.0
Range	51.0-683000.0	51.0-151354.0	256.0-683000.0	1.0-200000.0	1.0-683000.0
CEA (ng/mL)					
n	141	114	27	150	312
Median	77.7	66.1	125.7	129.5	92.0
Range	1.0-14515.0	1.0-14515.0	1.8-3069.0	1.7-12412.0	1.0-14515.0

Abbreviations: CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; MTC = medullary thyroid cancer; **MTC:-Cab/-Van** = Patients Not Previously Treated with Cabozantinib and/or Vandetanib; **MTC:+Cab/+Van** = Patients Previously Treated with Cabozantinib and/or Vandetanib; **MTC:NMD** = Patients with Non-Measurable Disease; **MTC:TrtNaïve** = Patients Naïve to Any Systemic Therapy; **MTC:TrtOther** = Patients Naïve to Cabozantinib and Vandetanib But Previously Treated with Other Systemic Therapy; N = number of patients; n = number of patients in specific category; RET = REarranged during Transfection.

Baseline Disease Characteristics

Table 8: Baseline Disease Characteristics - RET-Mutant MTC Efficacy Analysis Population Data Cutoff: 15 June 2021

	Primary Analysis Set	Subsets of Primary Analysis Set		Supportive Analysis Set	Total MTC[a] N=314
Parameter	**MTC:-Cab/-Van N=142**	**MTC:TrtNaive N=115**	**MTC:TrtOther N=27**	**MTC:+Cab/+Van N=151**	
Stage at Entry, n (%)					
I	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.3)
II	3 (2.1)	3 (2.6)	0 (0.0)	1 (0.7)	4 (1.3)
III	3 (2.1)	2 (1.7)	1 (3.7)	5 (3.3)	9 (2.9)
IV	132 (93.0)	107 (93.0)	25 (92.5)	141 (93.4)	293 (93.3)
Missing	4 (2.8)	3 (2.6)	1 (3.7)	3 (2.0)	7 (2.2)
Investigator reported history of metastatic disease, n (%)					
Yes	139 (97.9)	113 (98.3)	26 (96.3)	148 (98.0)	306 (97.5)
No	3 (2.1)	2 (1.7)	1 (3.7)	3 (2.0)	8 (2.5)
Time since initial diagnosis, months					
Median	54.4	50.8	85.1	70.9	65.3
Range	1.4-593.1	1.4-593.1	2.8-449.5	3.3-603.2	1.4-603.2
Time since metastatic disease, months					
n	139	113	26	148	306
Median	43.3	32.6	80.3	53.9	48.5
Range	0.5-593.1	0.5-593.1	2.8-341.5	0.5-299.9	0.5-593.1
At least 1 measurable lesion by Investigator, n (%)					
Yes	140 (98.6)	113 (98.3)	27 (100.0)	149 (98.7)	289 (92.0)
No	2 (1.4)	2 (1.7)	0 (0.0)	2 (1.3)	25 (8.0)
Sum of diameters at baseline by Investigator, mm					
n	140	113	27	149	289
Median	58.6	58.3	58.8	57.0	57.0
Range	10.0-270.0	10.0-270.0	12.0-144.0	10.0-191.0	10.0-270.0
RET Mutation Type, n (%)					
M918T	86 (60.0)	66 (57.4)	20 (74.1)	99 (65.6)	197 (62.7)
Extracellular Cysteine Mutation	33 (23.2)	28 (24.3)	5 (18.5)	24 (15.6)	65 (20.7)
V804 M/L	6 (4.2)	5 (4.3)	1 (3.7)	8 (5.3)	14 (4.5)
Other	17 (12.0)	16 (13.9)	1 (3.7)	20 (13.2)	38 (12.1)
Molecular Assay Type, n (%)					
NGS on Tumour	107 (75.4)	90 (78.3)	17 (63.0)	116 (76.8)	239 (76.1)
PCR	19 (13.4)	12 (10.4)	7 (25.9)	22 (14.6)	45 (14.3)
NGS on Plasma/Blood	7 (4.9)	7 (6.1)	0 (0.0)	5 (3.3)	13 (4.1)
Other	9 (6.3)	6 (5.2)	3 (11.1)	8 (5.3)	17 (5.4)

Abbreviations: L = leucine; M = methionine; MTC = medullary thyroid cancer; **MTC:-Cab/-Van** = Patients Not Previously Treated with Cabozantinib and/or Vandetanib; **MTC:+Cab/+Van** = Patients Previously Treated with Cabozantinib and/or Vandetanib; **MTC:TrtNaïve** = Patients Naïve to Any Systemic Therapy; **MTC:TrtOther** = Patients Naïve to Cabozantinib and Vandetanib But Previously Treated with Other Systemic Therapy; N = number of patients; n = number of patients in specific category; NGS = next generation sequencing; PCR = polymerase chain reaction; RET = REarranged during Transfection; T = threonine; V = valine.

[a] The total column is calculated from the presented **MTC:-Cab/-Van** (N=142) plus **MTC:+Cab/+Van** (N=151) as well as the **MTC:NMD** (N=21) Analysis Sets.

Sources: Table 8.9, Table 8.10

Prior Cancer Therapy

Table 9: Prior Cancer Therapy- RET-Mutant MTC Efficacy Analysis Population Data Cutoff: 15 June 2021

Parameter	Primary Analysis Set MTC:-Cab/-Van N=142	Subsets of Primary Analysis Set MTC:TrtNaive N=115	MTC:TrtOther N=27	Supportive Analysis Set MTC:+Cab/+Van N=151	Total MTC[a] N=314
Received prior systemic therapy, n (%)					
Yes	27 (19.0)	0 (0.0)	27 (100.0)	151 (100.0)	188 (59.9)
No	115 (81.0)	115 (100.0)	0 (0.0)	0 (0.0)	126 (40.1)
Type of prior systemic therapy,[b] n (%)					
Chemotherapy	5 (3.5)	0 (0.0)	5 (18.5)	16 (10.6)	21 (6.7)
Platinum	4 (2.8)	0 (0.0)	4 (14.8)	2 (1.3)	6 (1.9)
Taxane	2 (1.4)	0 (0.0)	2 (7.4)	3 (2.0)	5 (1.6)
Immunotherapy	5 (3.5)	0 (0.0)	5 (18.5)	13 (8.6)	18 (5.7)
Anti-PD-1/PD-L1 therapy	4 (2.8)	0 (0.0)	4 (14.8)	11 (7.3)	15 (4.8)
Anti-CTLA4 therapy	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.3)	5 (1.6)
Multikinase inhibitor	10 (7.0)	0 (0.0)	10 (37.0)	151 (100.0)	170 (54.1)
Cabozantinib	0 (0.0)	0 (0.0)	0 (0.0)	83 (55.0)	89 (28.3)
Vandetanib	0 (0.0)	0 (0.0)	0 (0.0)	119 (78.8)	123 (39.2)
Sorafenib	4 (2.8)	0 (0.0)	4 (14.8)	9 (6.0)	13 (4.1)
Lenvatinib	3 (2.1)	0 (0.0)	3 (11.1)	15 (9.9)	18 (5.7)
Other MKIs[c]	3 (2.1)	0 (0.0)	3 (11.1)	22 (14.6)	25 (8.0)
Other	8 (5.6)	0 (0.0)	8 (29.6)	12 (7.9)	21 (6.7)
Radioactive Iodine	2 (1.4)	0 (0.0)	2 (7.4)	0 (0.0)	3 (1.0)
mTOR inhibitor	1 (0.7)	0 (0.0)	1 (3.7)	4 (2.6)	5 (1.6)
VEGF/VEGFR inhibitor	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.3)
Hormonal therapy	1 (0.7)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.3)
Other systemic therapy[d]	4 (2.8)	0 (0.0)	4 (14.8)	9 (6.0)	13 (4.1)
Number of prior systemic regimens, n (%)					
0	115 (81.0)	115 (100.0)	0 (0.0)	0 (0.0)	126 (40.1)
1	22 (15.5)	0 (0.0)	22 (81.5)	72 (47.7)	102 (32.5)
2	5 (3.5)	0 (0.0)	5 (18.5)	37 (24.5)	43 (13.7)
≥3	0 (0.0)	0 (0.0)	0 (0.0)	42 (27.8)	43 (13.7)
Number of prior systemic regimens					
Median	0.0	0.0	1.0	2.0	1.0
Range	0-2	0-0	1-2	1-8	0-8
Best response to last systemic treatment, n (%)					
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	6 (4.2)	0 (0.0)	6 (22.2)	15 (9.9)	22 (7.0)
Stable disease	7 (4.9)	0 (0.0)	7 (25.9)	55 (36.4)	67 (21.3)
Progressive disease	6 (4.2)	0 (0.0)	6 (22.2)	36 (23.8)	42 (13.4)
Not evaluated	8 (5.6)	0 (0.0)	8 (29.6)	45 (29.8)	57 (18.2)
Prior radiotherapy, n (%)					
Yes	46 (32.4)	35 (30.4)	11 (40.7)	83 (55.0)	138 (43.9)
No	96 (67.6)	80 (69.6)	16 (59.3)	68 (45.0)	176 (56.1)
Prior cancer related surgery, n (%)					
Yes	119 (83.8)	97 (84.3)	22 (81.5)	136 (90.1)	273 (86.9)
No	23 (162)	18 (15.7)	5 (18.5)	15 (9.9)	41 (13.1)

Exposure

Table 10: Selpercatinib Dose Intensity MTC Safety Population and Overall Safety Population Data Cutoff: 15 June 2021

	MTC Safety Population N=319	Overall Safety Population N=796
Time on Treatment (months)		
Median	24.4	21.3
Minimum	0.2	0.1
Maximum	47.8	49.0
Relative Dose Intensity (%)		
Mean (standard deviation)	84.5 (19.2)	84.8 (19.1)
Median	95.0	94.5
Range	17.3-100.1	17.3-100.1
Relative Dose Intensity Categories, n (%)		
≥90%	188 (58.9)	468 (58.8)
75 to <90%	44 (13.8)	121 (15.2)
50 to <75%	64 (20.1)	145 (18.2)
<50%	23 (7.2)	62 (7.8)

Dose Modifications

Table 11: Dose Modifications in MTC Safety Population and Overall Safety Populations-Data Cutoff: 15 June 2021

	MTC Safety Population N=319	Overall Safety Population N=796
Dose reduction, n (%)		
Any	124 (38.9)	343 (43.1)
For AE	116 (36.4)	325 (40.8)
For other reason	21 (6.6)	47 (5.9)
Dose withheld, n (%)		
Any	228 (71.5)	580 (72.9)
For AE	200 (62.7)	510 (64.1)
For other reason	96 (30.1)	229 (28.8)
Dose increase, n (%)		
Any	61 (19.1)	182 (22.9)
Intra-patient escalation[a]	22 (6.9)	69 (8.7)
Re-escalation[b]	26 (8.2)	84 (10.6)
Other reason	22 (6.9)	51 (6.4)

Abbreviations: AE = adverse event; MTC = medullary thyroid cancer; N = number of patients; n = number of patients in specific category.

a Started at a lower dose during dose escalation that was subsequently increased.

b Re-escalation after a dose reduction.

Source: Table 8.16

Numbers analysed

At the DCO date, 314 patients with RET mutant MTC are included in the efficacy analysis as they had achieved at least 6 months of potential follow-up time from the first dose.

The primary efficacy analysis set to support the proposed first-line indication included 142 patients not previously treated with Cabozantinib and/or Vandetanib (MTC:-Cab/-Van patients); of these 115 patients were naïve to any systemic therapy (MTC:TrtNaive Patients);and 27 patients were naïve to Cabozantinib and Vandetanib but previously treated with other systemic therapy (MTC:TrtOther).

The main supportive analysis sets include:

o Patients previously treated with Cabozantinib and/or Vandetanib (N=151);

Patients in Cohort 6 (only 1 patient at the DCO), which was introduced in protocol version 8, are not included in the evaluation of efficacy as it is a different population of patients who have received prior treatment with a selective RET inhibitor.

Outcomes and estimation

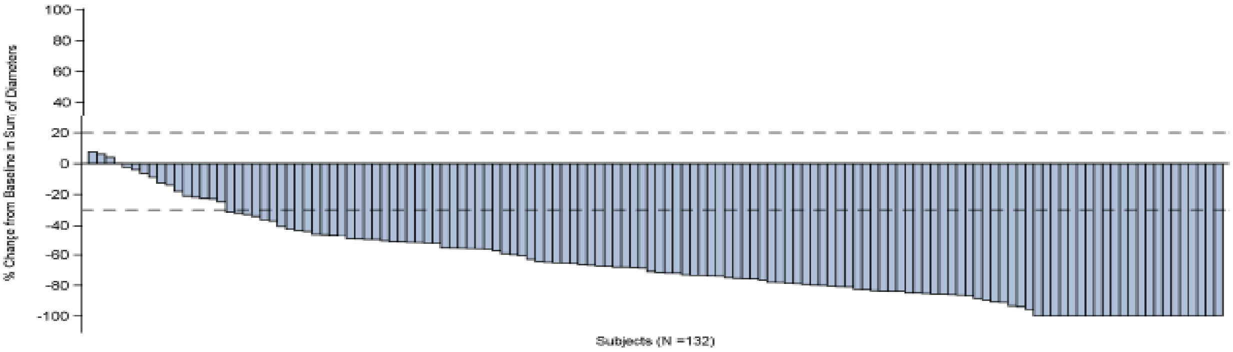
Cabozantinib and/or Vandetanib naïve mutant MTC: -Cab/-Van patients.

Objective Response Rate, Best Overall Response, Duration of Response and Clinical Benefit Rate

Table 12: Response Results RET-Mutant MTC Primary Efficacy Analysis Set (Data Cutoff Date: 15 June 2021)

	MTC:-Cab/-Van N=142	
	IRC Assessment	**Investigator Assessment**
Overall Response Rate[a]		
n (%)	115 (81.0)	110 (77.5)
95% CI[b]	73.6, 87.1	69.7, 84.0
Best Overall Response, n (%)		
Complete response (CR)	22 (15.5)	6 (4.2)
Partial response (PR)	93 (65.5)	104 (73.2)
Partial response, unconfirmed (uPR)	0 (0.0)	1 (0.7)
Stable disease (SD)	22 (15.5)	27 (19.0)
SD16+[c]	19 (3.4)	25 (17.6)
Progressive disease (PD)	2 (1.4)	1 (0.7)
Not evaluable	3 (2.1)	3 (2.1)
Clinical Benefit Rate (CR + PR+ uPR + SD16+[c])		
n (%)	134 (94.4)	136 (95.8)
95% CI[b]	89.2, 97.5	91.0, 98.4
Disease Control Rate (CR + PR + uPR + SD)		
n (%)	137 (96.5)	138 (97.2)
95% CI[b]	92.0, 98.8	92.9, 99.2
Duration of Response		
Responders, n	115	110
Median in months (95% CI)[d,e]	NE (NE, NE)	NE (NE, NE)
Censored n (%)	100 (87.0)	98 (89.1)
Reason Censored n (%)		
Alive without documented disease progression	94 (81.7)	91 (82.7)
Discontinued from study without documented PD	3 (2.6)	3 (2.7)
Died or documented PD after missing two or more consecutive visits	0 (0.0)	1 (0.9)
Discontinued treatment and lost to follow-up	3 (2.6)	3 (2.7)
Rate (%) of Duration of Response[d,f]		
12 months (95% CI)	91.9 (85.0, 95.7)	95.2 (88.9, 98.0)
24 months (95% CI)	83.7 (73.0, 90.4)	83.7 (72.1, 90.8)
36 months (95% CI)	76.7 (57.1, 88.2)	83.7 (72.1, 90.8)
Duration of Follow, Up (months)[e,g]		
Median	20.3	21.2
95% CI for median	17.7, 22.1	17.5, 23.1
25th, 75th percentiles	14.2, 25.8	13.8, 25.8

Figure 4. Waterfall plot of best change in tumour burden RET-mutant MTC Primary Efficacy Analysis Set (Data cut-off: 15 June 2021)



Abbreviations: MTC = medullary thyroid cancer; N = number of patients per population; RET = REarranged during Transfection.
For each subject, the best percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar.
Baseline is defined as the last available measurement prior to the first dose of selpercatinib.
Ten patients are not included because 7 have non-target lesions only and 3 do not have post-baseline target lesion measurements.
Source: F14.2.2.1

Time to Response and Time to Best Response

Table 13: Time to Response and Based on IRC and Investigator's Assessments RET-Mutant MTC Primary Efficacy Analysis Set (Data Cutoff Date: 15 June 2021)

	MTC:-Cab/-Van N=142	
	IRC Assessment	**Investigator Assessment**
Patients with Best Response of Confirmed CR or PR, n	115	110
Time to Response (months)[a]		
Median	3.5	3.5
25th, 75th Percentiles	1.8, 5.5	1.8, 5.4
Minimum, Maximum	0.7, 19.8	0.7, 22.1
Time to Response, n (%)		
<2 months	51 (44.3)	44 (40.0)
≥2 to 4 months	29 (25.2)	33 (30.0)
≥4 months	35 (30.4)	33 (30.0)
Time to Best Response (months)[b]		
Median	3.6	3.6
25th, 75th percentiles	1.8, 7.4	1.8, 5.6
Min, max	0.7, 34.0	0.7, 22.1
Time to Best Response, n (%)		
<2 months	43 (37.4)	42 (38.2)
≥2 to 4 months	24 (20.9)	31 (28.2)
≥4 months	48 (41.7)	37 (33.6)

Abbreviations: CR = complete response; IRC = Independent Review Committee; max = maximum; min = minimum; MTC = medullary thyroid cancer; **MTC:-Cab/-Van** = Patients Not Previously Treated with Cabozantinib and/or Vandetanib; N = number of patients; n = number of patients in specific category; PR = partial response; RET = REarranged during Transfection.

[a] Time to response is defined as 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 patient's best response is confirmed CR) or PR (if patient's best response is confirmed PR) that was subsequently confirmed.

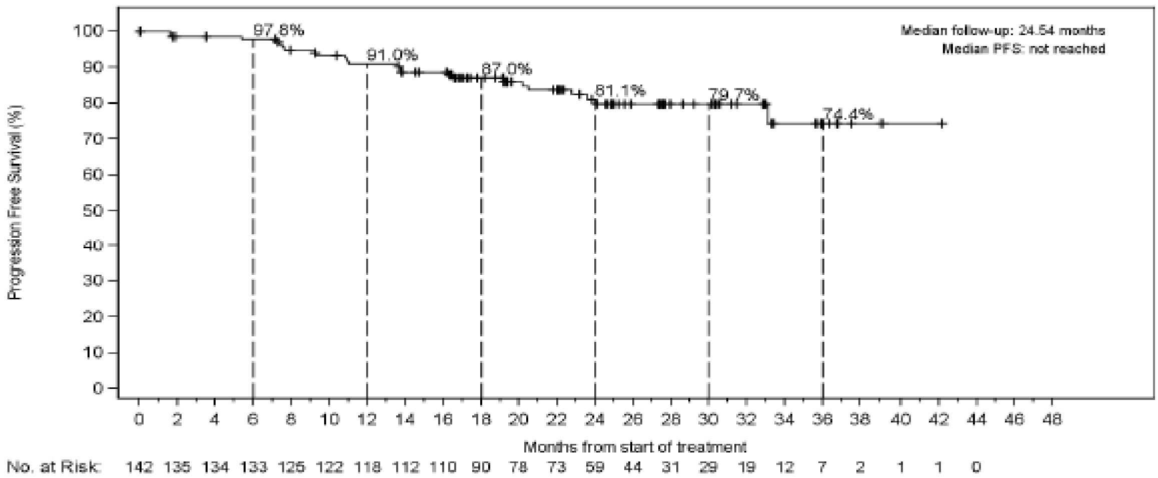
Sources: Table 8.22, Table 8.23

Progression Free Survival

Table 14: Progression-Free Survival Based on IRC and Investigator Assessment RET-Mutant MTC Primary Efficacy Analysis Set (Data Cutoff Date: 15 June 2021)

Status	MTC:-Cab/-Van N=142 IRC Assessment	MTC:-Cab/-Van N=142 Investigator Assessment
Progression Status, n (%)		
Disease progression	19 (13.4)	17 (12.0)
Died (no disease progression beforehand)	5 (3.5)	3 (2.1)
Censored	118 (83.1)	122 (85.9)
Reason Censored, n (%)		
Alive without documented disease progression	103 (75.2)	106 (74.6)
Subsequent anti-cancer therapy or cancer-related surgery without document progressive disease	5 (3.5)	3 (2.1)
Discontinued from study without documented progressive disease	5 (3.5)	6 (4.2)
Died or documented progressive disease after missing 2 or more consecutive visits	1 (0.7)	2 (1.4)
Discontinued treatment and lost to follow-up	4 (2.8)	5 (3.5)
Progression-Free Survival (months)[a,b]		
Median	NE	NE
95% CI for median	NE, NE	NE, NE
Min, max	0.0+, 42.2+	0.0+, 43.7+
Duration of Follow-Up (months)[b,c]		
Median	24.5	24.8
95% CI for median	22.0, 25.2	22.1, 27.3
25th, 75th percentiles	17.4, 30.2	17.2, 30.2
Rate (%) of Progression-Free Survival[a,d]		
12 months (95% CI)	91.0 (84.7, 94.8)	93.3 (87.6, 96.5)
24 months (95% CI)	81.1 (72.4, 87.3)	84.1 (75.6, 89.8)
36 months (95% CI)	74.4 (59.5, 84.5)	79.2 (67.4, 87.1)

Figure 5. Kaplan-Meier plot of progression-free survival based on IRC assessments – RET-mutant MTC Efficacy Analysis Set (Data cutoff: 15 June 2021)



Abbreviations: IRC = Independent Review Committee; MTC = medullary thyroid cancer; No. = number; + = Censored; PFS = progression-free survival; RET = REarranged during Transfection.
Source: F14.2.4.1

Overall Survival

Table 15: Overall Survival RET-Mutant MTC Primary Efficacy Analysis Set (Data Cutoff Date: 15 June 2021)

Status	MTC:-Cab/-Van N=142
Survival Status n (%)	
Died	8 (5.6)
Censored	134 (94.4)
Overall Survival (months)[a,b]	
Median	NE
95% CI for median	NE, NE
Min, max	1.9+, 44.4+
Duration of Follow-up (months)[b,c]	
Median	26.3
95% CI for median	24.3, 27.8
25th, 75th percentiles	20.7, 31.2
Rate (%) of Overall Survival[a,d]	
12 months (95% CI)	99.3 (94.9, 99.9)
24 months (95% CI)	95.0 (89.0, 97.7)
36 months (95% CI)	89.7 (76.2, 95.8)

Abbreviations: CI = confidence interval; max = maximum; min = minimum; **MTC:-Cab/-Van** = Patients Not Previously Treated with Cabozantinib and/or Vandetanib; N = number of participants in the specified category; NE = not estimable; RET = REarranged during Transfection.

[a] Estimate based on Kaplan-Meier method. + = Censored observation

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

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

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

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

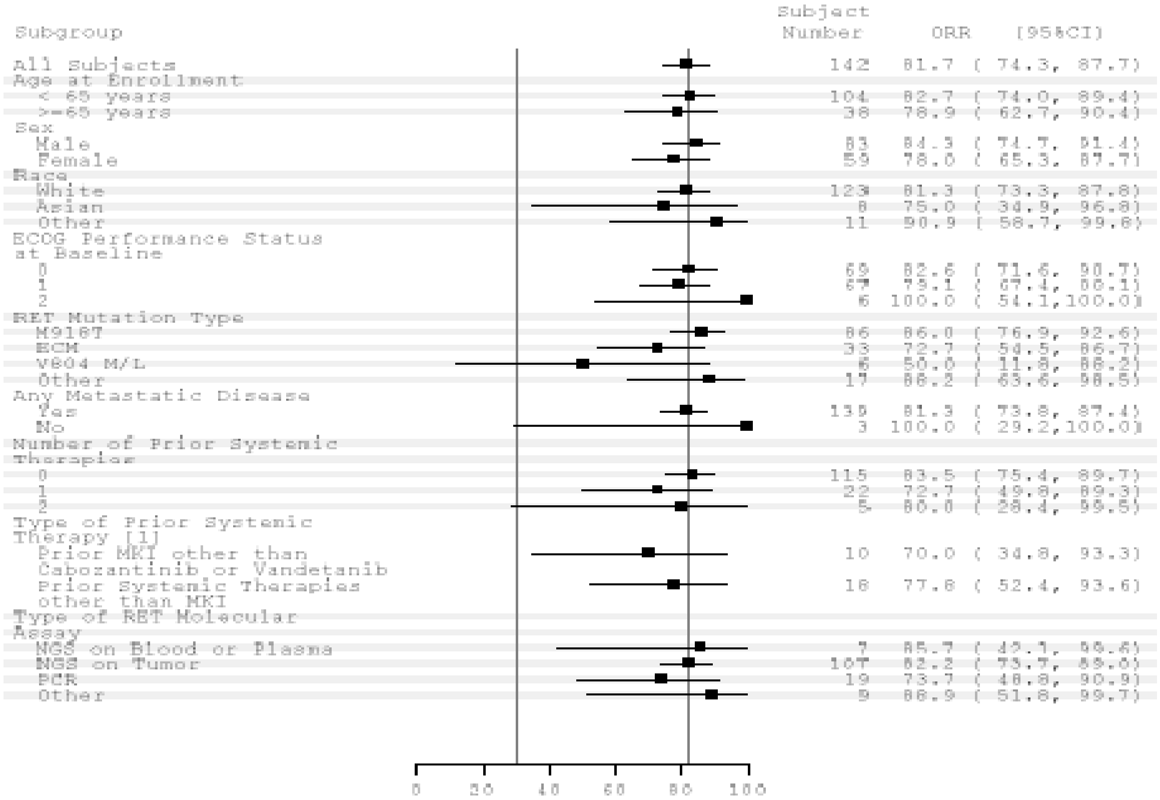
Data cutoff: 15 June 2021.

Source: Table 8.26

Ancillary analyses

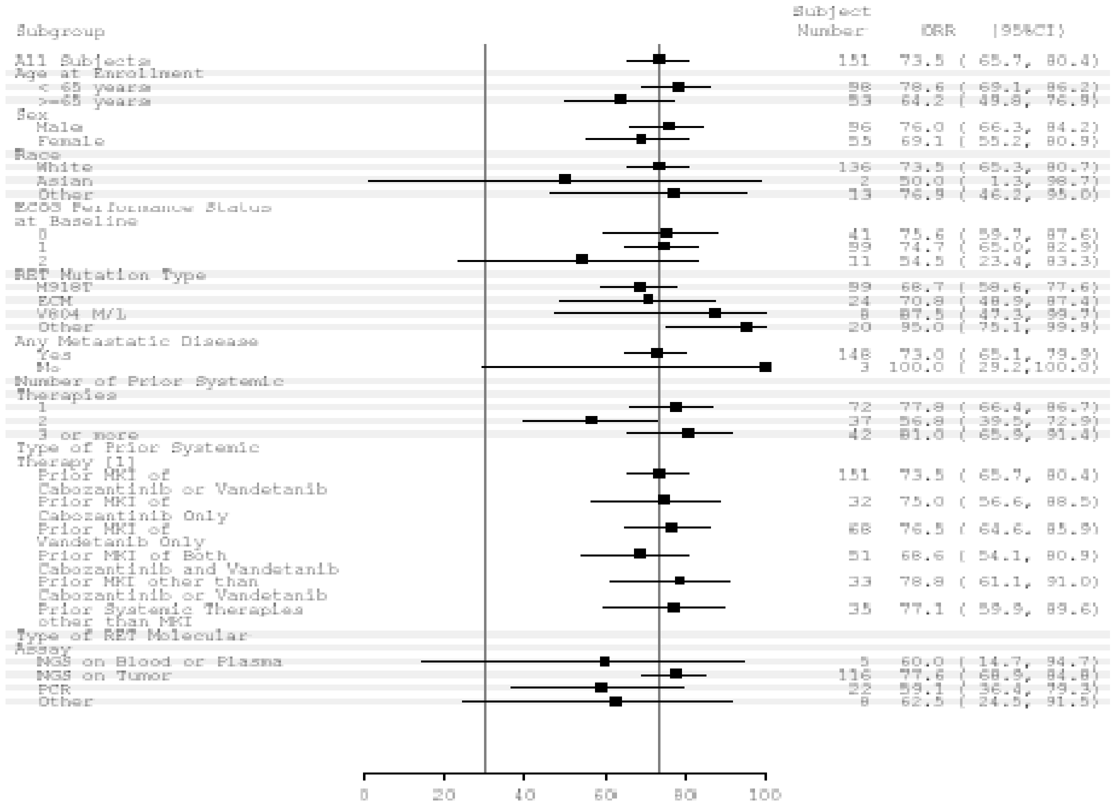
MTC:-Cab/-Van patients

Figure 6: Forest plot of objective response rate in special/subgroup populations by demographics and baseline characteristics based on IRC assessments in MTC:-Cab/-Van patients- data cutoff: 15 June 2021.



Abbreviations: IRC = Independent Review Committee; **MTC:-Cab/-Van** = Patients Not Previously Treated with Cabozantinib and/or Vandetanib.

Figure 7: Forest plot of objective response rate in special/subgroup populations by demographics and baseline characteristics based on IRC assessments in MTC:+Cab/+Van patients data cutoff: 15 June 2021.



Abbreviations: IRC = Independent Review Committee; **MTC:-Cab/-Van** = Patients Previously Treated with Cabozantinib and/or Vandetanib.

Summary of main study

The following table summarises 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 16. Summary of Efficacy for trial LIBRETTO-001

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; LIBRETTO-001		
Design	Phase 1/2, multicentre, open-label		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		ongoing not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Selpercatinib		Oral 10-, 20- or 80- mg capsules or 20 mg/mL suspension, QD or BID Dose escalation: 20 mg QD to 240 mg BID. Phase 2: 160mg BID
Endpoints and definitions	Primary endpoint	Objective response rate (ORR) by IRC	Proportion of patients with best overall response of confirmed complete response (CR) or confirmed partial response (PR) based on RECIST, 1.1.

	Secondary endpoint	Duration of Response (DOR) by IRC	The number of months from the start date of PR or CR, and subsequently confirmed, to the date of disease progression or death.
	Secondary endpoint	Progression Free Survival (PFS) by IRC	The number of months elapsed between the date of the first dose of selpercatinib and the earliest date of documented disease progression or death.
	Secondary endpoint	Overall Survival (OS)	The number of months elapsed between the date of the first dose of selpercatinib and the date of death.
Database lock	Not provided, DCO: 15 June 2021		

Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	**RET mutant MTC** **Cabozantinib/vandetanib treatment naïve** DCO: 15 June 2021	
Descriptive statistics and estimate variability	Treatment group	Selpercatinib
	Number of subject	142
	ORR % by IRC (95% CI)	115 (81) 73.6, 87.1
	DOR median, months by IRC	NE
	(95% CI)	NE,NE
	PFS median, months by IRC (95% CI)	NE NE, NE
	OS landmark rates (%) (95% CI)	99.3 (94.9, 99.9) at 12 months 95.0 (89.0, 97.7) at 24 months 89.7 (76.2, 95.8) at 36 months
Analysis description	**Prior cabozantinib/vandetanib treatment** DCO: 15 June 2021	
Descriptive statistics and estimate variability	Treatment group	Selpercatinib
	Number of subject	151
	ORR % by IRC	111 (73.5) (65.7, 80.4)
	DOR median, months (95% CI)	NE (27.2, NE)
	PFS median, months (95% CI)	34 (25.7, NE)
	OS landmark rates (%) (95% CI)	87.7 (81.2, 92.1) at 12 months 77.2 (69.3, 83.4) at 24 months 65.5 (53.7, 75.0) at 36 months
Effect estimate per comparison	Not applicable, single arm trial	
Notes	CI = confidence interval; NE = not estimable	

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
LIBRETTO-001 trial Total MTC Efficacy Population, N = 314	64/314	30/314	3/314

Supportive study

MTC: +Cab/+Van patients

Table 17: Response Results RET-Mutant MTC Supportive Efficacy Analysis Set

	MTC:+Cab/+Van N=151	
	IRC Assessment	**Investigator Assessment**
Overall Response Rate[a]		
n (%)	111 (73.5)	107 (70.9)
95% CI[b]	65.7, 80.4	62.9, 78.0
Best Overall Response, n (%)		
Complete response (CR)	14 (9.3)	7 (4.6)
Partial response (PR)	97 (64.2)	100 (66.2)
Partial response, unconfirmed (uPR)	0 (0.0)	1 (0.7)
Stable disease (SD)	31 (20.5)	33 (21.9)
SD16+[c]	27 (17.9)	28 (18.5)
Progressive disease (PD)	2 (1.3)	5 (3.3)
Not evaluable	7 (4.6)	5 (3.3)
Clinical Benefit Rate (CR + PR+ uPR + SD16+[c])		
n (%)	138 (91.4)	136 (90.1)
95% CI[b]	85.7, 95.3	84.1, 94.3
Disease Control Rate (CR + PR + uPR + SD)		
n (%)	142 (94.0)	141 (93.4)
95% CI[b]	89.0, 97.2	88.2, 96.8
Duration of Response		
Responders, n	111	107
Median in months (95% CI)[d,e]	NE (27.2, NE)	31.7 (26.1, NE)
Censored n (%)	77 (69.4)	69 (64.5)
Reason Censored n (%)		
Alive without documented disease progression	60 (54.1)	62 (57.9)
Subsequent anti-cancer therapy or cancer related surgery without PD	8 (7.2)	2 (1.9)
Discontinued from study without documented PD	5 (4.5)	3 (2.8)
Discontinued treatment and lost to follow-up	4 (3.6)	2 (1.9)
Rate (%) of Duration of Response[d,f]		
12 months (95% CI)	82.8 (74.1, 88.8)	80.7 (71.6, 87.1)
24 months (95% CI)	64.5 (52.9, 73.9)	61.9 (50.4, 71.5)
36 months (95% CI)	57.9 (44.0, 69.5)	48.7 (33.7, 62.2)
Duration of Follow-Up (months)[e,g]		
Median	22.9	23.0
95% CI for median	20.3, 25.4	19.3, 26.0
25th, 75th percentiles	17.5, 29.4	15.4, 29.2

Abbreviations: CI = confidence interval; MTC = medullary thyroid cancer; **MTC:+Cab/+Van** = Patients Previously Treated with Cabozantinib and/or Vandetanib; N = number of patients in population; n = number of patients per category; NE = not evaluable; ORR = objective response rate; RET = REarranged during Transfection; SD16 = stable disease lasting 16 or more weeks.

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 $\geq$28 days.

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

Table 18: Response on Last Prior Systemic Therapy Compared to Selpercatinib RET-Mutant MTC Supportive Efficacy Analysis Set

	MTC:+Cab/+Van N = 151		
	Best response to last systemic therapy n (%)	Best response to selpercatinib n (%)	p-value[a]
Responders	15 (9.9)	107 (70.9)	<0.0001
Complete Response	0 (0.0)	7 (4.6)	
Partial Response	15 (9.9)	100 (66.2)	
Non-Responders	136 (90.1)	44 (29.1)	
Partial Response, Unconfirmed	0 (0.0)	1 (0.7)	
Stable Disease	55 (36.4)	33 (21.9)	
Progressive Disease	36 (23.8)	5 (3.3)	
Not Estimated	45 (29.8)	5 (3.3)	

Abbreviations: MTC = medullary thyroid cancer; **MTC:+Cab/+Van** = Patients Previously Treated with Cabozantinib and/or Vandetanib; N = number of patients; n = number of patients in specific category; RET = REarranged during Transfection.

a McNemar exact test, assesses the significance of the difference between response rate for the last prior therapy versus response rate to treatment with selpercatinib.

Source: Table 8.31

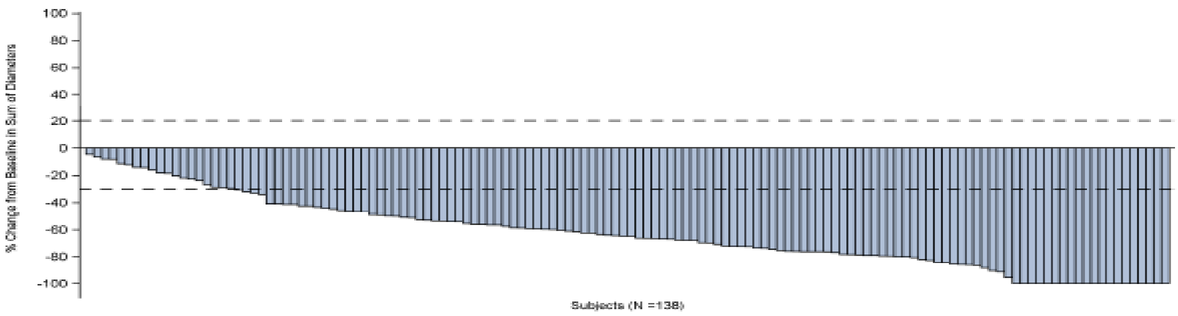
Table 19: Response on Last Prior Systemic Therapy Compared to Selpercatinib RET-Mutant MTC Supportive Efficacy Analysis Set

	MTC:+Cab/+Van N = 151
Patients responding to selpercatinib but not to prior therapy, n (%)	95 (62.9)
Patients responding to both selpercatinib and prior therapy, n (%)	12 (7.9)
Patients responding to prior therapy but not selpercatinib, n (%)	3 (2.0)
Patients who did not respond to selpercatinib or prior therapy, n (%)	41 (27.2)

Abbreviations: MTC = medullary thyroid cancer; **MTC:+Cab/+Van** = Patients Previously Treated with Cabozantinib and/or Vandetanib; N = number of patients in the population; n = number of patients per category; RET = REarranged during Transfection.

Source: flpritrt_mtc_ias_inv.csv

Figure 8. Best change in tumour burden RET-mutant MTC Supportive Efficacy Analysis Set. (Data cut-off: 15 June 2021)



Abbreviations: MTC = medullary thyroid cancer; N = number of patients per population; RET = REarranged during Transfection.
For each subject, the best percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar.
Baseline is defined as the last available measurement prior to the first dose of selpercatinib.
Thirteen patients are not included because 7 have non-target lesions only and 6 do not have post-baseline target lesion measurements.
Source: F14.2.2.1

Table 20: Time to Response and Time to Best Response Based on IRC and Investigator Assessments RET-Mutant MTC Supportive Efficacy Analysis Set

Status	MTC:+Cab/+Van N=151	
	IRC Assessment	Investigator Assessment
Patients with Best Response of Confirmed CR or PR, n	111	107
Time to Response (months)[a]		
Median	3.5	3.5
25th, 75th Percentiles	1.8, 5.5	1.8, 7.2
Minimum, Maximum	0.7, 26.6	0.7, 17.8
Time to Response, n (%)		
<2 months	43 (38.7)	46 (43.0)
≥2 to 4 months	32 (28.8)	19 (17.8)
≥4 months	36 (23.8)	42 (39.2)
Time to Best Response (months)[b]		
Median	3.7	3.7
25th, 75th percentiles	1.8, 5.6	1.8, 9.0
Min, max	0.7, 32.9	0.7, 27.8
Time to Best Response, n (%)		
<2 months	36 (32.4)	42 (39.3)
≥2 to 4 months	32 (28.8)	19 (17.8)
≥4 months	43 (28.5)	46.0 (42.9)

Abbreviations: CR = complete response; IRC = Independent Review Committee; max = maximum; min = minimum; MTC = medullary thyroid cancer; MTC:+Cab/+Van = Patients Previously Treated with Cabozantinib and/or Vandetanib; N = number of patients; n = number of patients in specific category; PR = partial response; RET = Rearranged during Transfection.

a Time to response is defined as 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 patient's best response is confirmed CR) or PR (if patient's best response is confirmed PR) that was subsequently confirmed.

Sources: Table 8.22, Table 8.23

Table 21: Progression-Free Survival Based on IRC and Investigator Assessment RET-Mutant MTC Supportive Efficacy Analysis Set

Status	MTC:+Cab/+Van N=151	
	IRC Assessment	Investigator Assessment
Progression Status, n (%)		
Disease progression	44 (29.1)	60 (39.7)
Died (no disease progression beforehand)	13 (8.6)	6 (4.0)
Censored	94 (62.3)	85 (56.3)
Reason Censored, n (%)		
Alive without documented disease progression	68 (45.0)	72 (47.7)
Subsequent anti-cancer therapy or cancer-related surgery without document progressive disease	11 (7.3)	4 (2.6)
Discontinued from study without documented progressive disease	11 (7.30	7 (4.6)
Discontinued treatment and lost to follow-up	4 (2.6)	2 (1.3)
Progression-Free Survival (months)[a,b]		
Median	34.0	33.4
95% CI for median	25.7, NE	24.7, NE
Min, max	0.0+, 42.2+	0.0+, 46.0+
Duration of Follow-Up (months)[b,c]		
Median	27.6	27.7
95% CI for median	24.9, 29.8	25.0, 30.3
25th, 75th percentiles	19.6, 33.2	21.9, 33.9
Rate (%) of Progression-Free Survival[a,d]		
12 months (95% CI)	78.7 (70.9, 84.6)	74.6 (66.7, 80.9)
24 months (95% CI)	64.4 (55.4, 72.0)	59.0 (50.2, 66.7)
36 months (95% CI)	48.3 (36.5, 59.1)	47.4 (36.9, 57.2)

Abbreviations: CI = confidence interval; IRC = Independent Review Committee; max = maximum; min = minimum; MTC = medullary thyroid cancer; MTC:+Cab/+Van = Patients Previously Treated with Cabozantinib and/or Vandetanib; N = number of patients; n = number of patients in specific category; NE = not estimable; RET = REarranged during Transfection.

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

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

c Estimate based on Reverse Kaplan-Meier method.

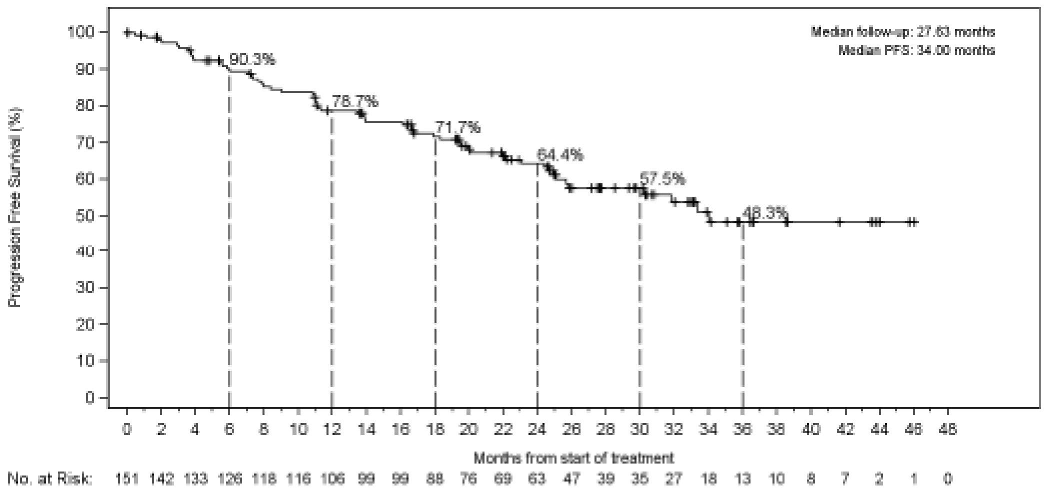
d 95% CI was calculated using Greenwood's formula.

Note: Efficacy eligible subjects are defined as the subjects whose first dose date is on or before 24 March 2021.

Data cutoff: 15 June 2021.

Sources: Table 8.24, Table 8.25

Figure 9. Kaplan Meier for progression-free survival based on IRC assessments RET-mutant MTC Supportive Efficacy Analysis Set.



Abbreviations: IRC = Independent Review Committee; MTC = medullary thyroid cancer; No. = number; + = Censored; PFS = progression-free survival; RET = REarranged during Transfection.
Source: F14.2.4.1

Table 22: Overall Survival RET-Mutant MTC Supportive Efficacy Analysis Set

Status	**MTC:+Cab/+Van N=151**
Survival Status n (%)	
Died	39 (25.8)
Censored	112 (74.2)
Overall Survival (months)[a,b]	
Median	NE
95% CI for median	NE, NE
Min, max	0.4+, 47.8+
Duration of Follow-up (months)[b,c]	
Median	28.8
95% CI for median	26.9, 30.5
25th, 75th percentiles	22.8, 34.5
Rate (%) of Overall Survival[a,d]	
12 months (95% CI)	87.7 (81.2, 92.1)
24 months (95% CI)	77.2 (69.3, 83.4)
36 months (95% CI)	65.5 (53.7, 75.0)

Abbreviations: CI = confidence interval; max = maximum; min = minimum; MTC = medullary thyroid cancer; **MTC:+Cab/+Van** = Patients Previously Treated with Cabozantinib and/or Vandetanib; N = number of participants in the specified category; n = number of patients in specific category; NE = not estimable; RET = REarranged during Transfection.

a Estimate based on Kaplan, Meier method. + = Censored observation

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

c Estimate based on Reverse Kaplan-Meier method.

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

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

Data cutoff: 15 June 2021.

Source: Table 8.26

Biochemical Response Rates for Calcitonin and CEA

Table 23: Biochemical Response Rate for Calcitonin and CEA RET-Mutant MTC Supportive Efficacy Analysis Set

Parameter	MTC:+Cab/+Van N=151	
	Calcitonin	CEA
Number of Biochemical Response Eligible Patients[a]		
n	148	146
Best Biochemical Response (n, %)[b]		
Complete response (CR)	41 (27.7)	22 (15.1)
Partial response (PR)	95 (64.2)	86 (58.9)
Stable disease (SD)	1 (0.7)	23 (15.8)
Progressive disease (PD)	2 (1.4)	8 (5.5)
Not evaluable (NE)	9 (6.1)	7 (4.8)
Not determined[c]	0 (0.0)	0 (0.0)
Biochemical Response Rate (CR + PR)[d]		
n (%)	136 (91.9)	108 (74.0)
95% CI	86.3, 95.7	66.1, 80.9
Time to Biochemical Response (months)[e]		
Median	0.5	1.0
25th, 75th percentile	0.5, 0.6	0.9, 3.6
Minimum, maximum	0.4, 6.2	0.4, 41.4
Time to Best Biochemical Response (months)[f]		
Median	0.5	1.8
25th, 75th percentile	0.5, 1.0	0.9, 3.7
Minimum, maximum	0.4, 16.5	0.5, 41.1

Other Supportive Efficacy Analysis Sets

Analysis	Efficacy Output	Location of Full Analysis
MTC:Initial+Cab/+Van		
ORR by IRC	70.9% (95% CI: 57.1, 82.4)	Table 8.18
Rate of DoR by IRC	12 mos: 86.3% (95% CI: 70.2, 94.1) 24 mos: 70.9% (95% CI: 52.5, 83.3) 36 mos: 63.2 (95% CI: 43.7, 77.5)	Table 8.20
TTR by IRC	mTTR: 3.7 mos	Table 8.22
Rate of PFS by IRC	12 mos: 82.3% (95% CI: 68.7, 90.4) 24 mos: 69.8 (95% CI:55.0, 80.6) 36 mos: 54.6 (95% CI: 38.7, 68.0)	Table 8.24
Rate of OS	12 mos: 86.9% (95% CI: 74.4, 93.5) 24 mos: 77.1% (95% CI: 63.2, 86.3) 36 mos: 69.4% (95% CI: 54.0, 80.6)	Table 8.26
MTC:NMD		
ORR by IRC	38.1% (95% CI: 18.1, 61.6)	Table 8.18
Rate of DoR by IRC	12 mos: 100.0% (95% CI: NE, NE) 24 mos: NE (95% CI: NE, NE) 36 mos: NE (95% CI: NE, NE)	Table 8.20
TTR by IRC	mTTR: 2.7 mos	Table 8.22
Rate of PFS by IRC	12 mos: 95.0% (95% CI: 69.5, 99.3) 24 mos: 95.0% (95% CI: 69.5, 99.3) 36 mos: NE (95% CI: NE, NE)	Table 8.24
Rate of OS	12 mos: 100.0% (95% CI: NE, NE) 24 mos: 100.0% (95% CI: NE, NE) 36 mos: NE (95% CI: NE, NE)	Table 8.26
MTC:TrtNaïve		
ORR by IRC	83.5% (95% CI: 75.4, 89.7)	Table 8.18
Rate of DoR by IRC	12 mos: 91.4% (95% CI: 83.5, 95.6) 24 mos: 84.5% (95% CI: 72.5, 91.6) 36 mos: 75.1% (95% CI: 49.7, 88.9)	Table 8.20
TTR by IRC	mTTR: 2.7 mos	Table 8.22
Rate of PFS by IRC	12 mos: 89.9% (95% CI: 84.2, 94.2) 24 mos: 81.6% (95% CI: 71.6, 88.4) 36 mos: 73.4% (95% CI: 52.2, 86.4)	Table 8.24
Rate of OS	12 mos: 99.1% (95% CI: 93.7, 99.9) 24 mos: 94.7% (95% CI: 87.5, 97.8) 36 mos: 88.8% (95% CI: 69.0, 96.3)	Table 8.26
MTC:TrtOther		
ORR by IRC	70.4% (95% CI: 49.8, 86.2)	Table 8.18

Analysis	Efficacy Output	Location of Full Analysis
Rate of DoR by IRC	12 mos: 94.4% (95% CI: 66.6, 99.2) 24 mos: 77.5% (95% CI: 43.6, 92.5) 36 mos: NE (NE, NE)	Table 8.20
TTR by IRC	mTTR: 5.5 mos	Table 8.22
Rate of PFS by IRC	12 mos: 96.2% (95% CI: 75.7, 99.4) 24 mos: 78.2% (95% CI: 54.9, 90.4) 36 mos: 72.2% (95% CI: 47.5, 86.7)	Table 8.24
Rate of OS	12 mos: 100.0% (95% CI: NE, NE) 24 mos: 96.0% (95% CI: 74.8, 99.4) 36 mos: 90.0% (95% CI: 64.6, 97.5)	Table 8.26
By-patient listing of efficacy outcomes based on INV assessments	NA	Individual Efficacy Response Data appendix
By-patient listing of efficacy outcomes based on IRC assessments	NA	Individual Efficacy Response Data appendix

Abbreviations: CI = confidence interval; DoR: duration of response; INV = investigator; IRC = Independent Review Committee; mos = months; **MTC:Initial+Cab/+Van** = The First 55 Patients Enrolled who were Previously Treated with Cabozantinib and/or Vandetanib; **MTC:NMD** = Patients with Non-Measurable Disease; **MTC:TrtNaïve** = Patients Naïve to Any Systemic Therapy; **MTC:TrtOther** = Patients Naïve to Cabozantinib and Vandetanib But Previously Treated with Other Systemic Therapy; mTTR = modified time-to-response; NE = not evaluable; PFS = progression-free survival; ORR = objective response rate; OS = overall survival; TTR = time-to-response.

Note: Median DoR not displayed in table because it was not reached for all analysis sets. See Table 8.20.

2.4.3. 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 medullary thyroid cancer (MTC) not previously treated with a RET inhibitor" is based on results from the ongoing study LOXO-RET-17001 (LIBRETTO-001) as of the cut-off date of 15 June 2021. This was an open-label, multicentre, phase 1/2 study which consisted on 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 NSCLC (1L/2L), MTC, and other tumours.

The Phase 1 portion of the study has been completed. The Phase 2 portion is ongoing and continuing to enrol patients with advanced solid tumours.

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. Amendments made on eligibility criteria since the initial submission of the CMA (DCO of June 2019) are not expected to have a substantial impact on study population or efficacy data. A new cohort, cohort 6, was introduced by amendment protocol (version 9) to include patients who discontinued another selective RET inhibitor because of intolerance. Efficacy data from patients with MTC in this cohort is not yet available and this was adequately reflected in the therapeutic indication.

The RP2D of selpercatinib (160 mg BID) was selected in Phase 1 and has been used as the starting dose for patients in the Phase 2 of the study. Patients continued selpercatinib dosing in 28-day cycles until PD, unacceptable toxicity, or other reason for treatment discontinuation. Patients with PD could continue selpercatinib if, in the opinion of the investigator, they deriving clinical benefit from continuing study treatment.

The primary efficacy endpoint was ORR based on RECIST v1.1. Given the uncontrolled design of the clinical trial, ORR could be an acceptable primary endpoint. PFS, OS and DOR were assessed as secondary endpoints. It is important to consider that even if results in term of ORR are outstanding, interpretation of benefit in term of survival endpoints is difficult and uncertain in uncontrolled setting. FDA censoring rules were used for DoR and PFS. Patients enrolled into the Phase 1 dose escalation as well as the Phase 1 and Phase 2 dose expansion cohorts were grouped to derive the analysis sets. Patients with RET-mutant MTC 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.

As of the 15 June 2021 data cutoff, 796 patients had been enrolled in the Phase 1 and Phase 2 cohorts and were treated with at least 1 dose of selpercatinib. Of these, 314 patients were RET mutant MTC and are considered eligible for efficacy analyses. Of the 314 efficacy eligible patients with RET-mutant MTC, 221 (70.4%) patients were still on treatment. The most common reason for treatment discontinuation for patients was PD (40 [12.7%]). A total of 21 patients (6.7%) discontinued treatment due to an AE.

Of the 142 MTC:-Cab/-Van patients, 83.1% of patients were still on treatment. The main reason for treatment discontinuation was AE (5.6%) followed by withdrawal of consent (4.2%).

Of the 151 MTC:+Cab/+Van patients, 57.0% of patients were still on treatment. The main reason for treatment discontinuation was progressive disease (23.2%) followed by AE (7.9%).

The MAH provides information on study conduct from Protocol version 8.0 up to Protocol version 9.0 (03 June 2020). Some of the changes introduced with Protocol v8 are the addition of a new cohort (Cohort 6) to allow the inclusion of patients previously treated with another RET-selective inhibitor with around 50 patients planned to be enrolled. Efficacy data from this cohort are not yet available. Moreover, with protocol v9 the number of patients to be enrolled in Cohort 1 and Cohort 5 is increased, in order to accommodate enrolment demand and allow for the characterization of AEs that may occur with low frequency.

A tabulated summary of important protocol deviations for RET-Mutant MTC safety population was provided The Applicant clarified that none of these deviations were considered to have a marked impact on safety or efficacy evaluations.

The MTC population is relatively young and could be considered representative of the disease as in most of the cases this is a hereditary condition of early onset. The median age for cab and van naïve patients was 57 years old, with patients enrolled from 15 up to 87 years old and the most numerous age group was 45 – 64 years. The total population under 18 years old were 2 patients. A total of 47.2% of patients had a baseline ECOG score of 1.

The majority of the MTC:-Cab/-Van patients were stage IV at the diagnosis. Median time from diagnosis to study entry was 54.4 months, which is line with relatively long survival of the disease. At study entry, almost all of the patients were metastatic and present at least one measurable lesion per investigator. Of the 142 MTC: -Cab/-Van patients, 115 patients (81%) were treatment naïve and 27 patients (19%) received prior systemic therapy including other therapies than cabozantinib and/or vandetanib (chemotherapy, immunotherapy, sorafenib, lenvatinib, radioactive iodine).

Regarding RET mutation, M918T was the most common mutation (60% of patients) although other less frequent mutations were also present (i.e. extracellular cysteine [23.2%], V804M/L [4.2%], and others [12%]). In most cases the method used for RET determination was NGS on tumour (75.4%), followed by PCR (13.4%).

The median time on treatment for the MTC safety population (N=319) was 24.4 months, ranging from 0.2 to 47.8 months. Concerning the dose exposure to selpercatinib, not all the patients reached the intended dose (160 mg BID). Median TOT was 24.4 months in the MTC Safety Population.

Baseline demographics and disease characteristics for patients previously treated with platinum based chemotherapy remain consistent with those provided at the DCO of June 2019.

Efficacy data and additional analyses

The evidence supporting of the claimed indication in first line Ret mutant MTC came from the 142 cab/van naïve patients. Of these –cab/-van, 115 patients were naïve to any systemic therapy (MTC:TrtNaive patients); and 27 patients were naïve to Cabozantinib and Vandetanib but previously treated with other systemic therapy (MTC:TrtOther).

Supportive evidence came mostly from the 151 patients previously treated with Cabozantinib and/or Vandetanib.

Cabozantinib and/or Vandetanib naïve mutant MTC: -Cab/-Van patients.

As of the cut-off date of 15 June 2021, the ORR among 142 -Cab/-Van naïve patients was 81.0%; (95% CI: 73.6, 87.1) by IRC and 77.5% (95%CI: 69.7, 84) by Investigator’s assessment. The overall concordance rate between IRC and Investigator assessments was 86.6%.

At the time of the DCO, 26 of the 58 responders (44.8%) had progressed or died. The median DOR by IRC assessment was not reached, with a median follow-up of 20.3 months (95% CI: 17.7, 22.1) with 81.7% of responders were still on treatment. The rate of DoR at 12 months was 91.9% (95% CI: 85.0, 95.7); at 24 months, 83.7% (95% CI: 73.0, 90.4).

The clinical benefit rate, defined as proportion of patients with a CR or PR, or SD lasting 16 or more weeks, was 94.4% (134 out of 142 patients; 95% CI: 89.2, 97.5).

The disease control rate, defined as proportion of patients with CR, PR, or SD (of any duration) as their best response, was 96.5% (137 out of 142 patients; 95% CI: 92.0, 98.8).

As determined by IRC assessment, the majority of patients demonstrated a reduction in tumour size from baseline. For the 115 responders in the RET-mutant MTC:-Cab/-Van, the median TTR and TTBR by IRC assessment was 3.5 months and 3.6 months, respectively.

Median PFS by IRC was not reached with a median follow-up of 24.5 months (95% CI: 22.0, 25.2). At the time of data cutoff, 75.2% of patients were still on treatment with no documented disease progression. The rate of PFS at 12 months was 91.0% (95% CI: 84.7, 94.8); at 24 months, 81.1% (95% CI: 72.4, 87.3).

Median duration of observed OS was not estimable with 90.1% of patients remaining alive at a median follow-up of 26.3 months (95% CI: 24.3, 27.8). The rate of OS at 12 months was 99.3% (95% CI: 94.9, 99.9), at 24 months was 95.0% (95% CI: 89.0, 97.7), and at 36 months was 89.7% (95% CI: 76.2, 95.8). The OS data is not yet considered mature.

The biochemical response rate for calcitonin was 95.1% (95% CI: 90.1, 98.0) and for CEA was 79.4% (95% CI: 71.6, 85.9).

Analysis by subgroups in MTC:-Cab/-Van patients did not reveal any remarkable difference to main analysis. Overall, ORR were mostly in line with the main analysis.

Prior +Cab/+Van MTC patients

The ORR in the 151 MTC:+Cab/+Van patients, was of 73.5% (95% CI: 65.7, 80.4) by IRC and 70.9% (95% CI: 62.9, 78.0) by Inv with a concordance rate of 80.1%. There was 14 CR (9.3%).

The median DoR by IRC assessment was not reached, with a median follow-up of 22.9 months (95% CI: 20.3, 25.4) with 54.1% of patients were still on treatment. The rate of DoR at 12 months was 82.8% (95% CI: 74.1, 88.8); at 24 months, 64.5% (95% CI: 52.9, 73.9). The mDOR by inv was 31.7 months (95%CI: 26.1, NE).

The CBR, was 91.4% (138 out of 151 patients; 95% CI: 85.7, 95.3) per IRC assessment. The ORR of 70.9% for selpercatinib (including 95 patients who did not achieve response on their last prior therapy), was remarkably higher than the ORR of 9.9% (n=15) for the last prior therapy.

The median TTR and TTBR by IRC assessment was 3.5 months and 3.7 months, respectively.

Estimated median duration of PFS by IRC was 34.0 months (95% CI: 25.7, NE) with a median follow-up of 27.6 months (95% CI: 24.929.8). At the time of data cutoff, 45.0% of patients by IRC assessment were still on treatment with no documented disease progression. The rate of PFS at 12 months was 78.7% (95% CI: 70.9, 84.6); at 24 months, 64.4% (95% CI: 55.4, 72.0). Observations based on Investigator assessments were in line with IRC assessments (33.4 months (95% CI: 24.7, NE))

Median OS was not reached with 67.5% of the patients remaining alive and continuing OS follow-up at a median follow-up time of 28.8 months (95% CI: 22.8, 34.5). The rate of OS at 12 months was 87.7% (95% CI: 81.2, 92.1), at 24 months was 77.2% (95% CI: 69.3, 83.4), and at 36 months was 65.5% (95% CI: 53.7, 75.0). The OS data is not yet considered mature.

The biochemical response rate for calcitonin was 91.9% (95% CI: 86.3, 95.7) and for CEA was 74.0% (95%

Overall results were consistent with those of the primary analysis that led to the initial CMA.

The efficacy results among the 27 patients who were naïve to Cabozantinib and Vandetanib but previously treated with other systemic therapy (MTC:TrtOther) are overall consistent with those of naïve to any systemic therapy (MTC:TrtNaive Patients).

Assessment of paediatric data on clinical efficacy

Selpercatinib is also intended to be used in adolescent patients (i.e. ≥12 years) with RET-mutant MTC. In the study LIBRETTO-001, a total of three adolescent patients (15, 16 and 17 years, respectively) were included. Since according to the PIP (P/0369/2019) at least 2 evaluable subjects must be included for the primary analysis this measure was considered compliant with the PIP. The proposed dose of selpercatinib in adolescent patients with MTC is the same as for adults (i.e. 160 mg BID). However, in the study LOXO-RET-18036, an ongoing study in paediatric patients, including adolescent patients, a dose of 92 mg/m^2 BID (with a maximum dose of 160 mg BID) was considered appropriate. Thus, further justification was requested on the selected dose for adolescent patients with MTC. In study LIBRETTO-001, the same dose was selected for adults and adolescent patients, since from the perspective of drug metabolism, patients 12 years or older can be considered adults. In the case of selpercatinib, it is mainly metabolized by CYP3A4, which by the age of 12 may have reached its adult level of expression. With regard to study LOXO-RET-18036 (LIBRETTO-121), in paediatric patients (6 to 21 years), the planned initial dose (i.e. 92 mg/m2 BID) is intended to result in a similar exposure than the 160 mg/m^2 in adults. The Applicant indicated that any new information, from study LIBRETTO-121 regarding dosing in younger patients will be applied if required.

Of these patients, 2 had a starting dose of 160 mg BID whereas 1 patient had a starting dose of 80 mg BID and escalated to 160 mg BID. Two patients achieved a partial response and 1 had a stable disease lasting longer than 16 weeks. All these 3 patients remain on treatment as of the cut-off date.

Differences in exposure for extreme body weights do not seem to have a worrying impact in safety based on data provided but the limited number of <50 kg patients included and duration of exposure make it hard to reach any final conclusion about dose adjustment recommendation in these low weight patients.

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 and in order to fulfil a CMA, a global phase 3 study is projected to complete enrolment by August 2023 (LIBRETTO 531 in RET-mutant MTC).

This phase 3 study will be conducted in patients with previously untreated *RET*-mutant MTC. As of 01 March 2022, the study is approximately 64% enrolled (161 of the planned initial 250 patients).

2.4.4. Conclusions on the clinical efficacy

The updated efficacy results from the ongoing phase 1/2 study LIBRETTO-001 in patients previously treated with cabozantinib and/or vandetanib are consistent with those provided in the original submission. For Cab/Van naïve patients (MTC:-Cab/-Van), the obtained ORR of 82% could be considered clinically meaningful. Although immature, K-M estimates for DOR, PFS and OS at several time-points are promising.

Since efficacy results are based on a single clinical trial with immature time-to-event endpoints, data corresponding to a longer follow-up are still required as well as efficacy results from the ongoing phase 3 study LIBRETTO-531 (the SOB study 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 RET fusion-positive NSCLC, RET fusion -positive thyroid cancer and RET mutant MTC, the MAH should submit the final study report from the pivotal study LIBRETTO-001 by 31 December 2023

- In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET-mutant MTC, the MAH should submit the clinical study report of the Phase 3 study J2G-MC-JZJB (LIBRETTO-531) comparing selpercatinib to physician’s choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naive, RET-mutant MTC. The CSR should be submitted by 30 September 2025.

2.5. Clinical safety

Introduction

Safety data are available from a total of 796 patients in the LIBRETTO 001 study which is still ongoing. Of these, 319 (~ 49%) had RET-mutant MTC and includes 142 (44.5%) who were cabozantinib and vandetinib naive. 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 24. Description of Safety Analysis Sets (data Cut-off: 15 June 2021)

Analysis Set Name	Analysis Set Description	SAP Name	Number of Patients per Analysis Set
Overall Safety Population	All patients who received at least 1 or more doses of selpercatinib regardless of diagnosis or line of therapy	OSAS	796
MTC Safety Population	All patients with *RET*-mutant MTC who received at least 1 dose of selpercatinib. This is a subset of the **Overall Safety Population**	MTC total	319
MTC:-Cab/-Van	Includes patients with *RET*-mutant MTC that have had no prior systemic therapy or have been treated with a prior systemic therapy besides cabozantinib and vandetanib	SAS1	142
MTC:TrtNaive	Patients naive to any systemic therapy. This analysis set is an ad-hoc subset of **MTC:-Cab/-Van**	SAS1 naive	115
MTC:TrtOther	Patients naive to cabozantinib and vandetanib but previously treated with other systemic therapy. This analysis set is an ad-hoc subset of **MTC:-Cab/-Van**	SAS1 pretreated	27
MTC:+Cab/+Van	Includes all patients with *RET*-mutant MTC previously treated with cabozantinib and/or vandetanib	IAS	156

Abbreviations: Cab = cabozantinib; IAS = integrated analysis set; MTC = medullary thyroid cancer; N = number of subjects in the analysis population; NMD = non-measurable disease; OSAS = overall safety analysis set; RET = REarranged during Transfection; SAS = safety analysis set; Trt = treatment; Van = vandetanib.

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 118 patients with MTC: -Cab/-Van) were still receiving selpercatinib and 77 patients (10%, including 10 patients with MTC: -Cab/-Van) were in follow-up, but off treatment.

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 MTC Safety Population was disease progression (12, 5%), followed by AE (6.9%).

In the MTC Safety Population, 96.6% patients received at least 1 dose of selpercatinib 160 mg BID and 90% patients had a selpercatinib starting dose of 160 mg.

Table 25: Treatment and study disposition (MTC Safety Population)

Status	Integrated (N=156)	SAS1 (N=142)	SAS1 Naïve (N=115)	SAS1 Pre-treated (N= 27)	Total MTC (N=319)
Treatment Status (n, %)					
Discontinued	66 (42.3)	24 (16.9)	19 (16.5)	5 (18.5)	94 (29.5)
Continuing	90 (57.7)	118 (83.1)	96 (83.5)	22 (81.5)	225 (70.5)
Reason Treatment Discontinued (n, %)					
Progressive Disease	35 (22.4)	5 (3.5)	2 (1.7)	3 (11.1)	40 (12.5)
Adverse Event	13 (8.3)	8 (5.6)	7 (6.1)	1 (3.7)	22 (6.9)
Intercurrent Illness Compromising Ability to Fulfill Protocol Requirements	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Requirement for Alternative Treatment	2 (1.3)	1 (0.7)	1 (0.9)	0 (0.0)	4 (1.3)
Investigator Withdrawal of Consent	3 (1.9)	6 (4.2)	6 (5.2)	0 (0.0)	10 (3.1)
Death	6 (3.8)	2 (1.4)	1 (0.9)	1 (3.7)	8 (2.5)
Other	6 (3.8)	2 (1.4)	2 (1.7)	0 (0.0)	9 (2.8)
Study Status (n, %)					
Discontinued	52 (33.3)	14 (9.9)	12 (10.4)	2 (7.4)	68 (21.3)
Continuing	104 (66.7)	128 (90.1)	103 (89.6)	25 (92.6)	251 (78.7)
Reason Study Discontinued (n, %)					
Withdrawal of Consent	9 (5.8)	6 (4.2)	6 (5.2)	0 (0.0)	16 (5.0)
Lost to Follow-Up	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Death	39 (25.0)	8 (5.6)	6 (5.2)	2 (7.4)	47 (14.7)
Other	3 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)

The median time on treatment was 21.3 and 24.4 months, respectively, for the Overall Safety Population and MTC Safety Population.

The most reported dose modification was dose withheld (72.9% in the Overall Safety Population and 71.5% in the MTC Safety Population) primarily attributed to adverse events (AEs) (40.8% in the Overall Safety Population and 36.4% in the MTC 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 26: Summary of Safety Trends- Overall Safety Population and MTC safety population

	MTC Safety Pop.		Overall Safety Pop.	
Data cut-off date	*March 2020 N=315*	Jun 2021 N=319	*March 2020 N=746*	Jun 2021 N=796
Any TEAEs, n (%), [IR]	*313 (99.4) [4118.4]*	318 (99.7) [3975.0]	*740 (99.2) [3474.2]*	795 (99.9) [3581.1]
Related to selpercatinib	*293 (93.0) [861.8]*	304 (95.3) [725.5]	*690 (92.5) [734.0]*	756 (95.0) [721.5]
Grade ≥3 TEAEs, n (%), [IR]	*196 (62.2) [111.5]*	229 (71.8) [81.3]	*470 (63.0) [118.5]*	572 (71.9) [90.8]
Related to selpercatinib	*96 (30.5) [35.3]*	127 (39.8) [28.1]	*239 (32.0) [39.7]*	307 (38.6) [31.0]
Serious TEAEs, n (%), [IR]	*97 (30.8) [35.1]*	135 (42.3) [27.7]	*262 (35.1) [43.4]*	353 (44.3) [33.7]
Related to selpercatinib	*20 (6.3) [5.9]*	28 (8.8) [4.5]	*62 (8.3) [8.3]*	87 (10.9) [6.6]
TEAEs leading to discontinuation,[a] n (%), [IR]	*15 (4.8) [4.3]*	23 (7.2) [3.6]	*45 (6.0) [5.8]*	64 (8.0) [4.6]
Related to selpercatinib	*6 (1.9) [1.7]*	13 (4.1) [2.0]	*16(2.1) [2.0]*	25 (3.1) [1.8]
Fatal TEAEs, n (%) [IR]	*8 (2.5) [2.3]*	14 (4.4) [2.2]	*25 (3.4) [3.2]*	45 (5.7) [3.2]
Related to selpercatinib	*0 (0.0) [0.0]*	1 (0.3) [0.2]	*0 (0.0) [0.0]*	1 (0.1) [0.1]

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IR = incidence rate; MTC = medullary thyroid cancer; n = number of patients in specific category; N = number of subjects in the analysis population; TEAE = treatment-emergent adverse event.

[a] Permanently discontinued.

Note: Severity grade assignment based on CTCAE (v4.03).

IR is 100 times the number of patients experiencing the adverse event divided by the event-specific exposure to treatment.

Percentage is calculated based on the number of patients in the column heading as the denominator.

TEAEs are defined as adverse events that start on or after the first administration of selpercatinib.

Summary of Treatment-Emergent Adverse Events-Overall Safety Population and MTC Safety Population

Analysis Set	MTC: -Cab/-Van N=142	MTC: TrtNaive[a] N=115	MTC: TrtOther[a] N=27	MTC: +Cab/+Van N=156	MTC Safety Pop. N=319	Overall Safety Pop. N=796
Data cut-off date	Jun 2021	Jun 2021	Jun 2021	Jun 2021	Jun 2021	Jun 2021
Any TEAEs, n (%)	142 (100.0)	115 (100.0)	27 (100.0)	155 (99.4)	318 (99.7)	795 (99.9)
Related to selpercatinib	139 (97.9)	112 (97.4)	27 (100.0)	145 (92.9)	304 (95.3)	756 (95.0)
Grade ≥3 TEAEs, n (%)	97 (68.3)	78 (67.8)	19 (70.4)	117 (75.0)	229 (71.8)	572 (71.9)
Related to selpercatinib	64 (45.1)	53 (46.1)	11 (40.7)	55 (35.3)	127 (39.8)	307 (38.6)
Serious TEAEs, n (%)	51 (35.9)	37 (32.2)	14 (51.9)	75 (48.1)	135 (42.3)	353 (44.3)
Related to selpercatinib	16 (11.3)	13 (11.3)	3 (11.1)	11 (7.1)	28 (8.8)	87 (10.9)
TEAEs leading to discontinuation, n (%)	8 (5.6)	7 (6.1)	1 (3.7)	14 (9.0)	23 (7.2)	64 (8.0)
Related to selpercatinib	6 (4.2)	5 (4.3)	1 (3.7)	7 (4.5)	13 (4.1)	25 (3.1)
Fatal TEAEs, n (%)	4 (2.8)	3 (2.6)	1 (3.7)	10 (6.4)	14 (4.4)	45 (5.7)
Related to selpercatinib	1 (0.7)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.3)	1 (0.1)

Abbreviations: Cab = cabozantinib; MTC = medullary thyroid cancer; N = number of subjects in the analysis population; n = number of patients in the specific category; TEAE = treatment-emergent adverse event; Trt =treatment; Van = vandetanib.
a Subset of MTC:-Cab/-Van population.

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 MTC Safety Population were *oedema*, *diarrhoea, fatigue*, *dry mouth*, *hypertension, AST increased, ALT increased, constipation, rash, nausea, abdominal pain, headache and blood creatinine increased.*

The most common Grade ≥3 TEAEs in both the Overall and MTC 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 common treatment-emergent serious adverse events (TE-SAEs) occurring in ≥2% of patients in both the Overall and MTC Safety Populations was pneumonia.

Serious adverse event/deaths/other significant events

Serious AEs

The most common serious TEAEs observed in both the **Overall Safety Population** and **MTC:-Cab/-Van** are shown in table below

Preferred Term[a]	MTC:-Cab/-Van N=142		Overall Safety Population N=796	
	All Causality n (%)	Related n (%)	All Causality n (%)	Related n (%)
Data cut-off date	Jun 2021	Jun 2021	Jun 2021	Jun 2021
Patients with treatment-emergent SAEs	51 (35.9)	16 (11.3)	353 (44.3)	87 (10.9)
Pneumonia	6 (4.2)	0 (0.0)	33 (4.1)	0 (0.0)
Pleural effusion	1 (0.7)	1 (0.7)	24 (3.0)	5 (0.6)
Abdominal pain	4 (2.8)	1 (0.7)	20 (2.5)	3 (0.4)
Dyspnoea	0 (0.0)	0 (0.0)	18 (2.3)	0 (0.0)
Hyponatraemia	1 (0.7)	0 (0.0)	18 (2.3)	0 (0.0)
Diarrhoea	3 (2.1)	1 (0.7)	15 (1.9)	3 (0.4)
Sepsis	0 (0.0)	0 (0.0)	13 (1.6)	0 (0.0)

Abbreviations: Cab = cabozantinib; MedDRA = Medical Dictionary for Regulatory Activities; MTC = medullary thyroid cancer; N = number of subjects in the analysis population; n = number of patients in the specific category; SAE = serious adverse event; TEAE = treatment-emergent adverse event; Van = vandetanib.

[a] Adverse events were coded using MedDRA (version 21.0).

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

The most common treatment-emergent serious adverse events (TE-SAEs) occurring in >2% of patients in the MTC (-Cab/-Van) Safety Populations were pneumonia, abdominal pain and diarrhoea.

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

Deaths

Table 27: Summary of deaths Overall Safety Population

	RET-mutant MTC (N=319) n (%)	RET Fusion-positive Thyroid (N= 54) n (%)	RET Fusion-positive NSCLC (N=356) n (%)	Overall Safety (N=796) n (%)
Within 28 Days of Last Dose	14 (4.4)	1 (1.9)	33 (9.3)	56 (7.0)
Disease Progression	2 (0.6)	1 (1.9)	15 (4.2)	19 (2.4)
Adverse Event	11 (3.4)	0 (0.0)	17 (4.8)	34 (4.3)
Other	1 (0.3)	0 (0.0)	1 (0.3)	3 (0.4)
More than 28 Days after Last Dose	33 (10.3)	7 (13.0)	78 (21.9)	137 (17.2)
Disease Progression	27 (8.5)	5 (9.3)	58 (16.3)	109 (13.7)
Adverse Event	3 (0.9)	1 (1.9)	6 (1.7)	10 (1.3)
Other	3 (0.9)	1 (1.9)	14 (3.9)	18 (2.3)

Percentage is calculated based on the number of patients in the column heading as the denominator.
Patient 401-024 had a grade 5 treatment-emergent adverse event with fatal outcome in the adverse event form, but primary death reason was disease progression.

Table 28: Summary of deaths Overall Safety Population and MTC (-Cab/-Van) Patients

	MTC:-Cab/-Van N=142	Overall Safety Population N=796
Data cut-off date	Jun 2021	Jun 2021
Within 28 days of the last dose, n (%)	3 (2.1)	56 (7.0)
Disease progression	0 (0.0)	19 (2.4)
Adverse event	3 (2.1)	34 (4.3)
Other	0 (0.0)	3 (0.4)
More than 28 days after the last dose, n (%)	5 (3.5)	137 (17.2)
Disease progression	2 (1.4)	109 (13.7)
Adverse event	1 (0.7)	10 (1.3)
Other	2 (1.4)[a]	18 (2.3)

Abbreviations: Cab = cabozantinib; MTC = medullary thyroid cancer; N = number of patients; n = number of patients in the specific category; Van = vandetanib.

[a] Other included: (1) unknown - patient stayed on treatment for 3.5 months, and death occurred 2.5 years after the last dose of selpercatinib, and (2) patient admitted to hospital with abdominal pain and blood in stool.

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

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 35.1% and 32.3% of patients in the MTC 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 MTC safety population (44.8%), 20% and 22% were Grade ≥3 in the Overall and MTC 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 MTC safety population (30.9% versus 15.3, 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 3 patients (0.9%) in the MTC 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 MTC (22.9%) Safety Populations. Most patients had TEAEs of Grade 1 or 2 in severity in both the Overall Safety (16.3%) and MTC safety (18.8%) 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 48.6%) and decreased white blood cell count (48.7% and 41.8%) in both the Overall Safety Population and the MTC Safety Population, respectively.

The highest incidence of any grade treatment-emergent serum abnormality was reported for calcium decreased (58.7 and 66.4 %), and albumin decreased (55.7% and 53.3%) in both the Overall Safety Population and the MTC 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 MTC Safety Populations.

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 (MTC:-Cab/-Van) were ALT increase, AST increased, diarrhoea, and hypertension.

The most frequently reported TEAEs leading to a dose reduction in 5% or more patients in both the Overall Safety Population and Treatment-Naïve Patients (MTC:-Cab/-Van) were ALT and AST increase.

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 Treatment-Naïve Patients (MTC:-Cab/-Van) no events leading to permanent discontinuation of selpercatinib were reported in more than 1 patient.

Post marketing experience

As of November 2021, Selpercatinib was approved in 36 countries including those in the EU, the US and Switzerland for treatment of patients with RET fusion-positive NSCLC, RET fusion-positive thyroid cancer and RET-mutant medullary thyroid cancer. Specific patient populations and dosing guidance vary by country. Cumulatively, up to the 08 November 2021, an estimated 1000 patients were exposed to selpercatinib worldwide. The data reported from the post marketing setting, is 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 November 2021 confirmed and supported the previously established favourable benefit-risk profile for selpercatinib in the currently approved indications.

2.5.1. Discussion on clinical safety

Safety was evaluated in patients in the Overall Safety Population (N=796) and in the MTC Safety Population (N=319) 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 24.4 months, respectively, for the Overall Safety Population and MTC Safety Population. In the Treatment-Naïve Population (n=142), the median treatment duration is 25.3 months (range: 0.2 to 44.4 months) and 83.8% of patients were on treatment for at least 24 months.

The median relative dose intensity was similar for the Overall Safety Population (94.6%) and the MTC Safety Population (95.0%).

The most reported dose modification was dose withheld (72.9% in the Overall Safety Population and 71.5% in the MTC Safety Population) primarily attributed to adverse events (AEs) (40.8% in the Overall Safety Population and 36.4% in the MTC 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 (MTC -Cab/-Van).

The most frequent TEAEs occurring in 30% or more patients in both the Overall Safety Population and Treatment-Naïve Patients (MTC -Cab/-Van) were oedema, and dry mouth.

The most frequent Grade ≥3 TEAEs reported in 5% or more patients in both the Overall Safety Population and Treatment-Naïve Patients (MTC -Cab/-Van) were *hypertension*, followed by *ALT increased* and *AST increased*.

The most frequent TESAEs reported in 2% or more patients both in the Overall Safety Population and Treatment-Naïve Patients (MTC -Cab/-Van) 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 a total of 8 patients (5.6%), including 3 patients who died of AE within 28 days of the last dose of selpercatinib. None in the MTC Safety Population were reported by the investigator as treatment-related.

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

The safety profile observed in the data from the 15 June 2021 cut-off 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 (MTC -Cab/-Van) and the Overall Safety Population.

Additional safety data needed in the context of a conditional MA

Additional safety data including comparative data will be provided as part of the studies imposed as specific obligations. Longer follow-up from LIBRETTO-001 will allow a better characterisation of the long-term safety and the randomised phase 3 study LIBRETTO-531 will allow a contextualisation of the safety data compared to the control arm.

2.5.2. Conclusions on clinical safety

The overall safety profile of selpercatinib in Treatment-Naïve Patients (MTC -Cab/-Van) is consistent with that of the Overall Safety Population. The updated results provided in this analysis show the safety profile of selpercatinib is consistent with that reported previously, even with longer duration of treatment.

The CHMP considers the following measures necessary to address the missing safety 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 RET fusion-positive NSCLC, RET fusion -positive thyroid cancer and RET mutant MTC, the MAH should submit the final study report from the pivotal study LIBRETTO-001 by 31 December 2023

- In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET-mutant MTC, the MAH should submit the clinical study report of the Phase 3 study J2G-MC-JZJB (LIBRETTO-531) comparing selpercatinib to physician's choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naive, RET-mutant MTC. The CSR should be submitted by 30 September 2025.

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 2.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

Safety concerns

Table 29: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Liver injury Cardiac arrhythmia due to QT prolongation Reproductive and developmental toxicities
Missing information	Exposure and safety in patients with severe hepatic impairment Exposure and safety in patients with cardiac impairment

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient to characterise the risks of the product.

Risk minimisation measures

Table 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: Not Applicable	**Additional pharmacovigilance activities:** Studies: 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:** Studies: 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:** 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	**Routine pharmacovigilance activities** **beyond adverse reactions reporting and** **signal detection:**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: Not Applicable	None **Additional pharmacovigilance activities:** Study: None

Routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1 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 MAH is seeking an extension of indication for Retsevmo (selpercatinib) as monotherapy for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) not previously treated with a RET inhibitor.

3.1.2. Available therapies and unmet medical need

No selective agents are approved specifically for patients with RET-mutant MTC as a first-line therapy; after first-line therapy, selpercatinib is the only selective RET inhibitor approved in the EU.

The unselective MKIs vandetanib and cabozantinib are approved for the treatment of patients with unresectable locally advanced or metastatic MTCs, in adults and including children over the age of 5 in the case of vandetanib, irrespective of the RET status and irrespective of prior treatment.

Table 30: Response and Survival Rates of Current Standard of Care in MTC

Therapeutic	Vandetanib		Cabozantinib	
Population	MTC (irrespective of *RET* mutation)[a]	*RET*-mutant MTC[a]	MTC (irrespective of *RET* mutation)[b]	*RET*-mutant MTC[c]
N on study drug	231	110	219	169
ORR,%	45	51.8	28	32
PFS (months)				
Median HR (95% CI)	NR[d] 0.46 (0.31, 0.69)	-	11.2 0.28 (0.19, 0.40)	15 0.23 (0.14, 0.38)

Abbreviations: CI = confidence interval; HR = hazard ratio; MTC = medullary thyroid cancer; N = number of subjects in the analysis population; NR = not reached; ORR = objective response rate; PFS = progression-free survival; RET = REarranged during Transfection.

a ZETA (Wells et al. 2012).

b EXAM (Elisei et al. 2013).

c EXAM (Sherman et al. 2016).

d Estimated using Weibull model to be 30.5 months.

3.1.3. Main clinical studies

Clinical safety and efficacy of selpercatinib in treatment-naive patients with advanced RET-mutant medullary thyroid cancer (MTC) are based on analyses of interim data from LIBRETTO-001 (LOXO-RET-17001).

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.

3.2. Favourable effects

At the data cut-off 15 June 2021, 142 MTC:-Cab/-Van patients were efficacy evaluable and the ORR was 81.0% (95% CI: 73.6, 87.1) by IRC and 77.5% (95% CI: 69.7, 84.0) by investigator assessment. 22 patients (15.5%) exhibited a confirmed CR and 93 patients (65.5%) experienced PR.

The median TTR was 3.45 months by IRC and 3.53 by investigator. The rate of DoR at 12 months was 91.9% (95% CI: 85.0, 95.7); at 24 months, 83.7% (95% CI: 73.0, 90.4). Median DoR was not reached with a median follow-up of 20.3 months (95% CI: 17.7, 22.1) by IRC and 21.2 months (95% CI: 17.5, 23.1) by investigator.

The median PFS (IRC) was not reached, with 17% events observed and median follow-up of 24.5 months (95% CI: 22.0, 25.2). The rate of PFS at 12 months was 91.0% (95% CI: 84.7, 94.8), at 24 months 81.1% (95% CI: 72.4, 87.3).

Median OS was not reached at the time of the DCO (5.6% of events observed). The rate of OS at 12 months was 99.3% (95% CI: 94.9, 99.9), at 24 months was 95.0% (95% CI: 89.0, 97.7), and at 36 months was 89.7% (95% CI: 76.2, 95.8). Efficacy of selpercatinib seems consistent across most important subgroups.

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).

Even though updated efficacy data have been provided for RET mutant MTC patients regardless of line therapy, the median DOR, OS and PFS continued to be not estimable. The KM estimates for time-to-event endpoints (PFS, OS) seem promising, but they remain immature.

These limitations will be addressed post authorisation with the submission of updated data and longer follow-up from the LIBRETTO-001 study and the conduct of LIBRETTO-531, a randomised phase III trial in patients with progressive, advanced, kinase inhibitor-naive, RET-mutant MTC.

3.4. Unfavourable effects

Safety data are available from a total of 796 patients in the LIBRETTO-001 study.

Safety was evaluated in patients in the Overall Safety Population (N=796) and in the MTC Safety Population (N=319) 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 24.4 months, respectively, for the Overall Safety Population and MTC Safety Population. In the Treatment-Naïve Population (n=142), the median treatment duration is 25.3 months (range: 0.2 to 44.4 months) and 83.8% of patients were on treatment for at least 24 months.

The median relative dose intensity was similar for the Overall Safety Population (94.6%) and the MTC Safety Population (95.0%).

The most reported dose modification was dose withheld (72.9% in the Overall Safety Population and 71.5% in the MTC Safety Population) primarily attributed to adverse events (AEs) (40.8% in the Overall Safety Population and 36.4% in the MTC 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 (MTC -Cab/-Van).

The most frequent TEAEs occurring in 30% or more patients in both the Overall Safety Population and Treatment-Naïve Patients (MTC -Cab/-Van) were oedema, and dry mouth.

The most frequent Grade ≥3 TEAEs reported in 5% or more patients in both the Overall Safety Population and Treatment-Naïve Patients (MTC -Cab/-Van) were hypertension, followed by ALT increased and AST increased.

The most frequent TESAEs reported in 2% or more patients both in the Overall Safety Population and Treatment-Naïve Patients (MTC -Cab/-Van) 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 a total of 8 patients (5.6%), including 3 patients who died of AE within 28 days of the last dose of selpercatinib. None in the MTC Safety Population were reported by the investigator as treatment-related.

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

3.5. Uncertainties and limitations about unfavourable effects

Data on long-term safety is lacking and will be provided post approval with updated data from LIBRETTO-001 and the randomised phase 3 study LIBRETTO-531.
Effects Table

Table 31: Effects Table for Retsevmo in RET-mutant medullary thyroid cancer (data cut-off: 15 June 2021)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Treatment-Naïve Patients (-Cab/-Van) (n= 142)						
ORR	rate	n % (95% CI)	115 (81.0) (73.6, 87.1)	NA	uncontrolled data	LIBRETTO-001
DOR	median	Months (95% CI)	NR (NE, NE)	NA	Immature and uncontrolled data	
PFS	median	Months (95% CI)	NE (NE, NE)	NA	Immature and uncontrolled data	
OS	OS landmark rates	(%) (95% CI)	99.3 (94.9, 99.9) at 12 months 95.0 (89.0, 97.7) at 24 months 89.7 (76.2, 95.8) at 36 months	NA	Immature and uncontrolled data	
Unfavourable Effects						
Treatment-Naïve Patients (-Cab/-Van) (n= 142)						
Any TEAEs Related to selpercatinib	rate	n (%)	142 (100) 139 (97.9)	NA	uncontrolled data	
Grade ≥3 TEAEs Related to selpercatinib	rate	n (%)	97 (68.3) 64 (45.1)	NA	uncontrolled data	
TEAEs leading to treatment discontinuation Related to selpercatinib	rate	n (%)	8 (5.6) 6 (4.2)	NA	uncontrolled data	
Serious TEAEs Related to selpercatinib	rate	n (%)	51 (35.9) 16 (11.3)	NA	uncontrolled data	
Fatal TEAEs Related to selpercatinib	rate	n (%)	4 (2.8) 1 (0.7)	NA	uncontrolled data	

Abbreviations: ORR: Objective Response Rate, DOR: Duration of Response, PFS: Progression Free Survival, OS: Overall Survival

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Data supporting this application are based on one single-arm trial (LIBRETTO-001), which 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 population with an unmet medical need as long as the effect observed in ORR is outstanding and durable.

For cabozantinib and/or vandetanib naïve patients, clinical data from a larger and more mature dataset of patients are available (median follow-up time of 21 months). The obtained ORR of 81% is considered meaningful in patients with RET-mutant MTC in first-line setting. Median DOR was not reached at a median follow-up time of 20.27 months and K-M estimates at landmark time points for PFS and OS allow to anticipate lasting benefits from treatment. The ORR benefit for the intended population was observed with selpercatinib regardless of the line of therapy.

Although, other approved front-line therapies with established benefit exist, efficacy with selpercatinib is considered compelling. Indirect comparisons of available results (KM estimates of PFS and OS) with selpercatinib against those reported with MKIs cabozantinib and vandetinib seem promising and give some support to the benefit of the treatment in the first line. The ORRs for selpercatinib are higher than those reported for cabozantinib and vandetinib. Although PFS and OS data are not yet mature, the median follow-up of 24.54 and 26.25 months, respectively, provide robust data of the 24 months PFS and OS landmark rates. The 24-month PFS landmark rate (with a PFS rate of 81.1% [95% CI: 72.4, 87.3]) exceeds median PFS for the cabozantinib study. The median follow-up time has not yet exceeded the estimated 30.5 months median PFS in the vandetinib study; however, the PFS rate for selpercatinib at 30 months was 79.7% (95% CI: 70.6, 86.3).

The safety profile observed in the data from the 15 June 2021 cut-off 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.

3.6.2. Balance of benefits and risks

The provided results from LIBRETTO-001 have shown efficacy in term of tumour shrinkage. Responses seem durable and independent of treatment line. However, given the remaining uncertainties mostly related to the uncontrolled design of the pivotal study, comparative data from the phase 3 study (LIBRETTO-531 or J2G-MC-JZJB) together with further follow-up data from the pivotal trial LIBRETTO-001 are required as confirmatory evidence (SOBs).

3.6.3. Additional considerations on the benefit-risk balance

As comprehensive data on the product are also not available in the first-line treatment of RET mutant MTC, 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 confirmatory data from the ongoing LIBRETTO-531 study, an open-label randomised phase 3 study comparing selpercatinib to physician's choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naive, RET-mutant MTC (J2G-MC-JZJB). This study is currently recruiting and the submission of the final clinical study report (CSR) is expected by 30 September 2025. As of 01 March 2022, the study is approximately 64% enrolled (161 of the planned initial 250 patients) with approximately 60% of patients coming from EU countries. An extension of indication to include the first-line treatment of patients with MTC is not expected to have an impact on study recruitment. Results of the LIBRETTO-531 study are intended to provide a comprehensive data package and potentially convert the conditional MA into a full MA. There are currently supply constraints related to sourcing of vandetanib (Caprelsa) in the EU due to limited stock availability from the MAH. At this time, there has been no impact to patient treatment, nor is it anticipated that treatment will be impacted (even though amendments to the CTA have been submitted to mitigate any potential impact).
- Unmet medical need will be addressed, as selpercatinib is a selective treatment showing a response rate of such a magnitude that a clinical benefit would be expected compared to first line available unselective MKI options, vandetanib and cabozantinib. A major therapeutic advantage over existing therapies can therefore be concluded. In addition, selpercatinib has a differential safety profile compared to existing therapies with a significantly lower rate of TEAEs leading to permanent treatment discontinuation.
- 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.

3.7. Conclusions

The overall B/R of Retsevmo for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC) not previously treated with a RET inhibitor is positive subject to the specific obligations and conditions imposed in order to obtain further clinical data to generate a comprehensive clinical data set and 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 group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations 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 and IIIB

C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	Type IB	None

Extension of indication to include first-line treatment of advanced RET-mutant medullary thyroid cancer (MTC) in adults and adolescents 12 years and older based on interim results from Study LIBRETTO-001 (LOXO-RET-17001) on the clinical safety and efficacy of selpercatinib in patients with RET-mutant MTC who are cabozantinib and vandetanib treatment-naïve (MTC:-Cab/-Van). LIBRETTO-001 is a global, multicohort, open-label, Phase 1/2 study in adult and adolescent patients with advanced RET-altered tumours. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted.
As part of the application the MAH is requesting a 1-year extension of the market protection.
The application also includes an updated Phase II Environmental Risk Assessment in order to reflect the patient population as per the approved indication.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, IIIB and to the Risk Management Plan are recommended.

There are no new conditions but this recommendation is subject to the following specific obligations in Annex II:

Description	Due date
- In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive NSCLC, RET fusion -positive thyroid cancer and RET mutant MTC, the MAH should submit the final study report from the pivotal study LIBRETTO-001 by	31 December 2023
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET-mutant MTC, the MAH should submit the clinical study report of the Phase 3 study J2G-MC-JZJB (LIBRETTO-531) comparing selpercatinib to physician’s choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naive, RET-mutant MTC. The CSR should be submitted by	28 February 2025

Similarity with authorised orphan medicinal products

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

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers, that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Retsevmo-II/0014/G

Attachments

1. SmPC Package Leaflet (changes highlighted), as a relevant example with changes highlighted as adopted by the CHMP on 21 July 2022.

Appendices

1. CHMP AR on similarity dated 21 July 2022
2. CHMP AR on the significant clinical benefit in comparison with existing therapies dated 21 July 2022

1.