10 December 2020
EMA/9037/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Retsevmo

International non-proprietary name: selpercatinib

Procedure No. EMEA/H/C/005375/0000

Note

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

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

Abbreviation or Term	Definition
ULN	upper limit of normal
US	United States
US FDA	United States Food and Drug Administration
VEGF	vascular endothelial growth factor
Vz/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman of child-bearing potential
ADP90	action potential duration at 90 % repolarisation
ALT	alanine aminotransferase
ALP	Alkaline phosphatase
aq	aqueous
AST	Aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC0-24	area under the curve time from 0 to 24 hour
AUC0-t	area under the curve from 0 to last measurable concentration
BID	bis in die; twice a day
CHMP	Committee for Medicinal Products for Human use
CHO	Chinese hamster ovary
Cmax	maximum plasma concentration
Ca	calcium
CBPI	cytokinesis-blocked proliferation index
CFR	Code of Federal Regulations
cm	centimeter
CMC	carboxymethyl cellulose
CNS	central nervous system
cP	centipoise
CQA	Critical Quality Attribute
CV	cardiovascular
DAPI	4,6-diamidino-2-phenylindole
dL	deciliter
DMSO	dimethyl sulfoxide
DRF	dose range finding
DSI	Data Sciences International
DSC	Differential Scanning Calorimetry
DVS	dynamic vapor sorption
EC50	half-maximal effective concentration

ECG	electrocardiogram
EFD	embryo foetal development
ELISA	enzyme-linked immune absorbent assay
ER	oestrogen receptor
EU	European Union
F	female
FDA	Food and drug Administration
FGFR	fibroblast growth factor receptors
FIB	fibrinogen
FOB	functional observational battery
FRET	fluorescence resonance energy transfer
g	gram
GALT	Gut-associated lymphoid tissue
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GC	Gas Chromatography
GD	gestation day
GIT	gastrointestinal tract
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HEK293	human embryonic kidney cells
hERG	human ether-à-go-go related gene
h/hr	hour
HNSTD	highest non-severely toxic dose
HPBL	human peripheral blood lymphocytes
HPLC	High performance liquid chromatography
HTRF	Homogeneous Time Resolved Fluorescence
IC50	half maximal inhibitory concentration
ICH	International Council for Harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
INN	International Nonproprietary Name
IR	Infrared
IV	intravenous
J	joule
Ka	rate constant for association of enzyme and substrate
Kd	rate constant for dissociation of enzyme and substrate
KD	dissociation constant
KF	Karl Fischer titration
kg	kilogram
Km	Michaelis constant; the substrate concentration at which half a receptor’s active sites are occupied by substrate

L	liter
LC-MS	liquid chromatography-mass spectrometry
LDPE	Low Density Polyethylene
LLS	Laser Light Scattering
LMA	locomotor activity assessment
M	Male
M	Moles
µg	microgram
µL	microliter
µM	micromolar
MEC	molar extinction coefficient
MET	mesenchymal epithelial transition factor
mg	milligram
Mg	magnesium
MHC-I	major histocompatibility complex class I
mJ	millijoule
MKI	multi-kinase inhibitor
mL	milliliter
mm3	cubic millimeters
mol	mole
MnPCEs	micronuclei
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
MPE	mean photo effect
n	number
NA	not applicable
NCE	normochromatic erythrocytes
NDA	new drug application
ng	nanogram
NGS	next generation sequencing
nM	nanomolar
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOEL	no observed effect level
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
mM	millimolar
OD	optical density
OECD	Organization for Economic Co-operation and Development
PBPK	Physiologically based pharmacokinetic

PCE	polychromatic erythrocytes
PD	physeal dysplasia
PO	orally
pRET	phosphorylated RET
PD-1	programmed cell death protein 1
PDX	patient derived xenograft
POC	percent of control
PTC	papillary thyroid cancer
QC	Quality Control
QD	quaque die; once a day
QTc	Heart rate corrected QT
%RE	percent relative error
RBCs	red blood cells
RET	rearranged during transfection
RTK	receptor tyrosine kinase
Sa-XL665	Streptavidin-XL665
SD	standard deviation; Sprague-Dawley
SDS	sodium dodecyl sulfate
SmPC	Summary of Product Characteristics
STD 10	severely toxic dose in 10% of animals
SEM	standard error of the mean
TGA	Thermo-Gravimetric Analysis
TK	toxicokinetics
TK-AB-Cryptate	tyrosine kinase antibody-cryptate
TK-substrate biotin	biotinylated universal tyrosine kinase substrate
U	unit
US	United States
USP/NF	United States Pharmacopoeia/National Formulary
UV	ultraviolet
UVA	long wave ultraviolet A
	long wave ultraviolet B
USAB	United Sates Adopted Names
WT	wild type
w/v	Weight per volume
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 20 December 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Selpercatinib Lilly, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2019.

The applicant applied for the following indication:

Selpercatinib Lilly as monotherapy is indicated for the treatment of adults with:

– advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy

– advanced RET fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior treatment

Selpercatinib Lilly as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0369/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0369/2019 was 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 applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance selpercatinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific Advice/Protocol Assistance on the development relevant for the approved indications from the CHMP, on 25 July 20119 (EMEA/H/SA/4170/1/2019/PA/III, EMEA/H/SA/4170/2/2019/II). The Scientific Advice pertained to the following non-clinical, quality and clinical aspects of the dossier:

- The proposed starting material for the synthesis of selpercatinib, the proposed drug substance stability approach, and the proposed drug product packaging and stability;
- The adequacy of the non-clinical package, and specifically investigation of embryo-foetal developmental toxicity studies, to support MAA;
- 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, the proposed primary analysis and supplementary analyses sets for efficacy, and the inclusion of a TKi-naïve subgroup.
  - Regarding the RET-fusion NSCLC cohort, the adequacy of the proposed RET-fusion NSCLC patient population, the proposed primary analysis and supplementary analyses sets for efficacy, and the inclusion of a previously untreated subgroup.
  - The adequacy of the proposed datasets to support a benefit/risk assessment in RET-mutant MTC and RET-fusion NSCLC.
- 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;
- The design of the proposed Phase 3 study J2G-MC-JZJC in previously untreated RET-fusion NSCLC, 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: Blanca Garcia-Ochoa

The application was received by the EMA on	20 December 2019
The procedure started on	30 January 2020

The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 May 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 May 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	11 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 May 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 May 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	02 October 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 October 2020
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	15 October 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	09 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	02 December 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Selpercatinib Lilly on	10 December 2020
The CHMP adopted a report on similarity of Retsevmo product with cabozantinib and sorafenib on (Appendix 1)	10 December 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant is seeking a Marketing Authorisation for the following indications:

Treatment of adult patients with:

– advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy

– advanced RET fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior treatment

Treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy.

2.1.2. Epidemiology and risk factors

RET fusion-positive non-small cell lung cancer (NSCLC)

Approximately 85% to 90% of lung cancers are non-small cell lung cancer (NSCLC) and include 3 main subtypes: squamous cell, carcinoma, adenocarcinoma, and large cell (undifferentiated) carcinoma (Perez-Moreno et al. 2012; LCRF 2019). From all NSCLC cases, approximately 1% to 2% are expected to harbour a chromosomal rearrangement that produces a rearranged during transfection (RET) gene fusion and subsequently an oncogenically activated RET receptor tyrosine kinase (RTK) (Kohno et al. 2013; Kato et al. 2017; Ferrara et al. 2018).

In Europe, approximately 500,000 patients developed lung cancer in 2019 (LUCE 2019). Assuming 90% of these new cases are NSCLC (450,000), and *RET* fusions are present in 1% to 2% of European descendent NSCLC patients the incidence of new cases of *RET*-fusion protein lung cancer is expected to be around 4,500 to 9,000 per year (ESMO 2019).

While smoking and exposure to outdoor air pollution are known risk factors for NSCLC, they may not predict for *RET* fusion-positive NSCLC, given that patients with *RET* fusion-positive lung cancer have often been associated with never-smoker status.

RET-mutant medullary thyroid cancer (MTC)

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.

MTC accounts for 5% to 10% of all thyroid cancers, with 70% to 80% occurring as a sporadic entity (sMTC) and 25% as familial MTC (fMTC). Familial MTC can occur as fMTC alone or as part of multiple endocrine neoplasia type 2 (MEN2) (Figlioli et al. 2013). The majority of MTCs are sporadic, with about 10% identified as hereditary due to a germline activating mutation in the RET gene. Most sporadic MTCs also have activating RET mutations (Figlioli et al. 2013). Medullary thyroid cancer accounts for 13.4% of all thyroid cancer-related deaths (Figlioli et al.2013).

The typical age of presentation of sporadic MTC is in the fifth or sixth decade, with a slight preponderance in females. In contrast, MEN2A and fMTC typically present in the third decade of life, and MEN2B usually presents in those younger than age 20 (Roy et al. 2013). At presentation, 35% to 50% of patients with MTC have regional metastasis, while 13% to 15% have distant metastasis mainly to the lung, bone, and liver (Priya et al. 2017).

In Europe, an estimated 53,000 patients developed thyroid cancer in 2012. Assuming 5% of those cases were MTC (2,650), and assuming RET-mutations are present in 60% of MTC patients the incidence of new cases of RET-mutant MTC was approximately 1590 per year (ENRC 2019; Roskoski and Sadeghi-Nejad 2018).

MTC is very uncommon in children, but is most commonly associated with one of the multiple endocrine neoplasia (MEN) syndromes

RET-Fusion Positive Thyroid Cancer (TC)

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

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

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

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

2.1.3. Biologic features

Genetic alterations in the RET gene have been implicated in the pathogenesis of several human cancers. RET can become oncogenically activated through two primary mechanisms: 1) chromosomal rearrangements that fuse the RET kinase domain with a partner protein dimerisation domain (e.g., Coiled-coil domain-containing protein 6 (CCDC6)/papillary thyroid cancer-1 (PTC1), Kinesin Family Member 5B (KIF5B), NCOA4/PTC3), producing hybrid proteins that endow the kinase with ligand-independent, constitutive activity; and 2) point mutations that directly or indirectly activate the kinase (Drilon et al. 2018).

2.1.4. Clinical presentation, diagnosis <and stage/prognosis

RET fusion-positive non-small cell lung cancer (NSCLC)

RET fusion-positive lung cancer is associated with identifiable clinic pathologic characteristics, including younger age, never-smoker status, early lymph node metastas poor differentiation, and a solid-predominant subtype; RET rearrangement seems to be mutually exclusive with other driver mutations (e.g., EGFR, ROS1, KRAS mutations) (Bronte et al. 2019). Patients with RET fusion-positive lung cancer commonly have brain metastases at rates similar to the overall NSCLC population, in approximately 20-50% patients (Fenske et al. 2017; Drilon et al. 2018).

Most patients with NSCLC present with advanced stage, unresectable disease, and poor prognosis, with 5-year survival rates ranging from 10% to < 1% for Stage 4 (Planchard et al. 2018 ;). The symptoms associated with advanced NSCLC represent a significant burden to patients, and include dyspnoea, cough, fatigue, anxiety, depression, insomnia, and pain (Thompson et al. 2005;).

RET-mutant medullary thyroid cancer (MTC)

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. Medullary thyroid cancer can present at late stages and does not respond to thyroid stimulating hormone suppression or iodine, conferring reduced survival compared with thyroid cancer overall (Machens et al. 2014).

MTC may have an intermediate or severe prognosis accounting for a larger proportion of deaths attributed to thyroid cancer (Dal Maso et al. 2017). In Europe, the 5-year relative survival for patients with MTC was 88% (women) and 85% (men) (Dal Maso et al. 2017). The 10-year OS rate of patients with localised disease is approximately 95%, while that of patients with regional stage disease is about 75%. Only 20% of patients with distant metastases (13% to 15% of the MTC population) at diagnosis survive 10 years after diagnosis (Priya et al. 2017).

In paediatrics, MTC is most frequently associated with a family history of MEN2A, and children typically receive the diagnosis in the presymptomatic phase secondary to a family history of a known RET mutation transmitted in an autosomal dominant pattern of inheritance (Hanley et al. 2016).

RET-Fusion Positive Thyroid Cancer (TC)

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

In comparison to adults, children more often present with aggressive, advanced stage disease. This is at least in part due to the underlying biologic and molecular differences between paediatric and adult thyroid cancer. Specifically, papillary thyroid carcinoma (which accounts for approximately 90% of paediatric thyroid cancer) has a high rate of gene fusions (50-60%, compared to approximately 15% seen in adults), are associated with more extensive extrathyroidal disease (Starenki and Park 2015).

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

2.1.5. Management

RET fusion-positive non-small cell lung cancer (NSCLC)

Although patients with *RET* fusion-positive NSCLC have an identifiable driver mutation, they currently receive the same standard-of-care treatment as patients with NSCLC who do not have a driver mutation, as there are no *RET*-specific approved therapies.

Approved second-line chemotherapy treatments such as docetaxel alone or with ramucirumab, or single-agent pemetrexed Immune checkpoint inhibitors in monotherapy such as nivolumab, pembrolizumab, and atezolizumab are also used in this setting.

RET-mutant medullary thyroid cancer (MTC)

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 et al. 2015).

No systemic agents are approved specifically for patients with advanced *RET*-mutant MTC, who are treated with standard of care for MTC. Two available multikinase inhibitors (MKIs) **cabozantinib** and **vandetanib**, which have received regulatory approval for advanced MTC, irrespective of the presence or absence of a *RET* mutation.

RET-Fusion Positive Thyroid Cancer (TC)

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

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

About the product

Selpercatinib Selpercatinib is a potent and highly selective inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase. Selpercatinib inhibited wild type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3.

The CHMP adopted a positive opinion for use of Retsevmo in the following indications:

Retsevmo as monotherapy is indicated for the treatment of adults with:

- advanced *RET* fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy
- advanced *RET* fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

Retsevmo therapy should be initiated and supervised by physicians experienced in the use of anti-cancer therapies.

RET testing

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.

Posology

The recommended dose of Retsevmo based on body weight is:

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

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

Treatment should be continued until disease progression or unacceptable toxicity.

The current selpercatinib dose should be reduced by 50% if co-administering with a strong CYP3A inhibitor. If the CYP3A inhibitor is discontinued, the selpercatinib dose should be increased (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

Dose adjustments

Management of some adverse reactions may require dose interruption and/or dose reduction. Retsevmo dose modifications are summarised in Error! Reference source not found. **and**

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Table 1: **Recommended Dose Reductions for Retsevmo for Adverse Reactions**

Dosage Modification	Adults and Adolescents ≥50 Kg	Adults and Adolescents <50 Kg
Starting Dose	160 mg orally twice daily	120 mg orally twice daily
First Dose Reduction	120 mg orally twice daily	80 mg orally twice daily
Second Dose Reduction	80 mg orally twice daily	40 mg orally twice daily
Third Dose Reduction	40 mg orally twice daily	Not applicable

Table 2: **Recommended Dose Modifications for Adverse Reactions**

Adverse Drug Reaction		Dose modification
Increased ALT or AST	Grade 3 or Grade 4	• Suspend dose until toxicity resolves to baseline (see sections 4.4 and 4.8). Resume at a dose reduced by 2 levels. • If after at least 2 weeks selpercatinib is tolerated without recurrent increased ALT or AST, increase dosing by 1 dose level. • If selpercatinib is tolerated without recurrence for at least 4 weeks, increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT. • Permanently discontinue selpercatinib if Grade 3 or 4 ALT or AST increases recur despite dose modifications.

Hypersensitivity	All Grades	• Suspend dose until toxicity resolves and begin corticosteroids at a dose of 1 mg/kg (see sections 4.4 and 4.8). Resume selpercatinib at 40 mg twice daily while continuing steroid treatment. Discontinue selpercatinib for recurrent hypersensitivity. • If after at least 7 days, selpercatinib is tolerated without recurrent hypersensitivity, incrementally increase the selpercatinib dose by 1 dose level each week, until the dose taken prior to the onset of hypersensitivity is reached. Taper steroid dose after selpercatinib has been tolerated for at least 7 days at the final dose.
QT Interval Prolongation	Grade 3	• Suspend dose for QTcF intervals >500 ms until the QTcF returns to <470 ms or baseline (see section 4.4). • Resume selpercatinib treatment at the next lower dose level.
	Grade 4	• Permanently discontinue selpercatinib if QT prolongation remains uncontrolled after two dose reductions or if the patient has signs or symptoms of serious arrhythmia.
Hypertension	Grade 3	• Patient blood pressure should be controlled before starting treatment. • Selpercatinib should be suspended temporarily for medically significant hypertension until controlled with antihypertensive therapy. Dosing should be resumed at the next lower dose if clinically indicated (see sections 4.4 and 4.8).
	Grade 4	• Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled.
Haemorrhagic events	Grade 3 or Grade 4	• Selpercatinib should be suspended until recovery to baseline. • Discontinue selpercatinib for severe or life-threatening haemorrhagic events.
Other adverse reactions	Grade 3 or Grade 4	• Selpercatinib should be suspended until recovery to baseline. • Discontinue selpercatinib for severe or life-threatening events

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that:

- the unmet medical in part of the claimed indications was not established due to the different treatment alternatives available for these populations with proven benefit in terms of PFS/OS.

- whether selpercatinib was able to address any potential UMN could not been concluded.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data. The applicant recognises the importance of ensuring completion of the Phase 3 studies to confirm the benefit-risk observed in LIBRETTO-001 and proposes to provide regular updates on the enrolment and progress of the studies throughout the review process.

Planned Phase 3 Studies:

- Study J2G-MC-JZJB (LIBRETTO-531) is a global, multicentre, randomised (2:1), open-label, Phase 3 study comparing selpercatinib to physician's choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naive, RET-mutant MTC. Approximately 400 patients will be enrolled to the study. Endpoints of primary consideration are treatment failure-free survival (TFFS) and PFS. Secondary endpoints include ORR, DOR, OS and PFS2. TFFS is the primary endpoint and will serve as a gatekeeper to the evaluation of PFS. More specifically, PFS is type I error-controlled and will be assessed independently of and after assessment of TFFS, and only if TFFS achieves statistical significance. PFS will be the endpoint used for regulatory decision making.

- Study J2G-MC-JZJC (LIBRETTO-431) is a global, multicentre, randomised (2:1), open- label, controlled Phase 3 study of selpercatinib compared to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC. Approximately 250 participants will be randomly assigned to study intervention such that at least 140 PFS events will be observed. The primary endpoint is PFS and secondary endpoints include ORR, DOR, OS, and PFS2.

- Unmet medical needs will be addressed, as the data available demonstrate that selpercatinib provides a significant therapeutic benefit to patients with RET alterations.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. The benefits to public health based on the ability of selpercatinib to provide benefit in refractory patients, and a meaningful advance over available first-line therapies, represents a major public health interest.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 40 mg or 80 mg of selpercatinib as active substance.

Other ingredients (capsule content) are: cellulose microcrystalline and silica colloidal anhydrous.

For the capsule shell, excipients are: gelatin, titanium dioxide (E171), iron oxide (E172) (40 mg only), brilliant blue FCF (E133) (80 mg only).

For the capsules black ink, excipients are: shellac, ethanol (96 per cent), isopropyl alcohol, butanol, propylene glycol, water purified, ammonia solution, concentrated, potassium hydroxide, iron oxide black.

The product is available in a HDPE bottle containing 60 capsules or 120 capsules (80 mg only) as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General Information

The chemical name of selpercatinib is 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile corresponding to the molecular formula $C_{29}H_{31}N_7O_3$. It has a relative molecular mass of 525.61 g/mol and the following structure:

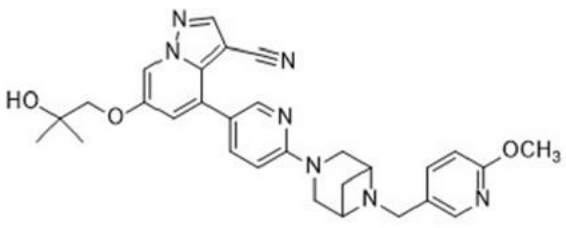


Figure 1. Active substance structure

The active substance is a slightly hygroscopic powder. Selpercatinib has a pH-dependent solubility profile. Solubility is highest in acidic media and decreases as pH increases. The active substance has a non-chiral molecular structure.

The characterisation of the active substance and its impurities are in general in accordance with the EU guideline on chemistry of new active substances and the ICH guidelines on impurities. The chemical structure of selpercatinib active substance was elucidated by a combination of mass spectrometry measurements, UV and infrared (IR) analysis, nuclear magnetic resonance (NMR) analysis (including chemical shift assignments and proton to carbon connectivity assignments), and elemental analysis. The solid-state properties of the active substance were measured by X-ray powder diffraction (XRPD), DSC, dynamic vapor sorption (DVS), and thermogravimetric analysis (TGA).

Polymorphism has been observed for the selpercatinib active substance. The selpercatinib active substance polymorphic form was identified and found suitable to be used as the commercial active substance. The control strategy ensures the correct polymorphic form.

Selpercatinib is not the subject of a monograph in the Ph. Eur.

Manufacture, process controls and characterisation

Selpercatinib is manufactured from well-defined starting materials with acceptable specifications. The proposed starting materials that are custom synthesised material and introduced in the penultimate chemical step of the proposed synthetic route were initially not considered acceptable by CHMP. A major objection was raised requesting redefinition of the initially proposed starting materials as intermediates and defining the starting materials at an earlier point in the synthesis to ensure that enough steps are conducted under GMP to appropriately mitigate risks associated with future changes to the starting materials' synthetic routes, unless sound justification was given to support that the proposed control strategy is adequate. In response, the applicant provided additional information and an in-depth discussion to confirm that the selection of the proposed starting materials in the proposed synthesis for selpercatinib active substance meets the requirements given in ICH Q11 and ICH Q11 Q&A. Specifications for both starting materials have been revised as requested. The description of the analytical methods used and summaries of the validation data have been provided.

A detailed discussion regarding the specificity of the impurity determining methods for the starting materials was submitted. An acceptable explanation, demonstrating the specificity issue noted in the HPLC method for the impurities in one of the starting materials is not a cause for concern, was provided. Adequate control of these impurities is ensured, in an indirect manner, in a downstream step. Concerning the impurities that show the same retention time, no discussion is provided in the response. Nevertheless, the information provided for genesis and fate and the control strategy overview for structurally related impurities was deemed sufficient to ensure an acceptable control of these impurities.

Taking into account that the critical steps (i.e. those that impact the active substance impurity profile) are included in the selpercatinib manufacturing process, no impurity from two of the starting materials persists to the active substance and acceptable specifications are proposed for both materials were considered acceptable starting materials. The applicant has confirmed that the starting material suppliers use the same route of synthesis.

Initially, CHMP raised concerns about the control strategy for one of the proposed starting materials. In response, the applicant addressed the concerns raised. The acceptance limit for an impurity in the specifications has been tightened. The capability of the process to purge this impurity, as confirmed in the fate and purge studies, and the manufacturing batch history support the proposed acceptance limit. A further test for another impurity has been added to the specifications. The limit proposed has been properly justified. The description and a validation summary of the analytical methods used for the control of the starting material have been submitted and found acceptable.

Information about the impurities with demonstrated specificity in the impurity determining GC method is given. All structurally related impurities potentially present have been included. The suitability of the specifications to control batches manufactured by the proposed processes has been adequately justified. Analytical data for batches have been provided as requested.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

It was initially stated that no critical process parameters have been determined in the active substance manufacturing process (i.e. all process parameters were categorized as non-critical process parameters), however the data presented were not sufficient to support this. In addition, proven acceptable ranges (PARs) for many of these process parameters were proposed in each step but initially they were not adequately justified. In response to questions raised by CHMP additional data was submitted by the applicant to support the proposed PARs. In addition, the applicant has clarified that any movement within a PAR range will occur only when other parameters are held at their target values, consistent with the definitions provided in ICH Q8 guideline on Pharmaceutical Development and EMA/CHMP/CVMP/QWP/354895/2017. Considering the studies performed and the clarifications provided, the proposed PARs were considered acceptable. The optimized parametric target value/set-point were defined in the manufacturing process for each step.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes introduced have been presented in sufficient detail. Data demonstrating the absence of changes in the polymorphic form of selpercatinib manufactured by earlier processes and commercial process were provided.

The active substance is packaged in LDPE which complies with the European Regulation 10/2011/EC, as amended and with Ph. Eur. Section 3.1.3, Polyolefins. Two container closure systems are proposed for the active substance. A third one is used in the stability study (LDPE liner (inner primary liner) and cable tied. This first liner was then placed into a second LDPE liner and the second liner was cable tied. This double LDPE package was then placed inside a mini-HDPE drum with a plastic closure). Data demonstrating equivalence of the 3 container closure systems from an active substance stability point of view were provided and found acceptable.

Specification

The active substance specification includes tests for identity (IR), crystal form (XRPD), assay (HPLC), impurities (HPLC), residual solvents (HSGC), description (visual), water content (KF/Ph. Eur.), particle size (LLS) and residue on ignition (Ph. Eur.).

Considering the recommendations given in the ICH Q6A and the properties of the active substance, the tests included in the active substance specifications are adequate. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The absence of control of parameters such as elemental impurities and microbiological control has been adequately justified.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of the active substance are provided for 4 pilot scale batches for one manufacturer and 2 pilot scale batches and 1 production scale batch for the other manufacturer. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three batches of active substance stored in a container closure system representative of that intended for the market for up to 12 months under long term conditions (25ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The active substance was packed in low-density polyethylene (LDPE) primary contact liners and placed into small high-density polyethylene (HDPE) drums to mimic bulk active substance storage at the time of manufacture. These batches were manufactured by a process representative of the commercial manufacturing process. In addition, additional supportive stability data were provided.

Photostability testing results were provided. These data support the stability of the active substance to light. Samples of selpercatinib active substance were subjected to stress testing at conditions of heat and humidity in alignment with ICH Q1A. No significant degradation was observed for solid samples stressed at 70°C/20% RH and 70°C/75% RH for up to 21 days. These results conclude that selpercatinib active substance would be chemically stable when stored at ambient temperature and humidity.

The applicant commits to place on stability three production batches of selpercatinib active substance manufactured at commercial scale. The proposed post-approval stability protocol is considered acceptable.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product contains 40 mg or 80 mg active substance (selpercatinib) and excipients in hard gelatin capsules.

The 40 mg is a size 2 (6 x 18 mm) gray opaque capsule with black “Lilly”, “3977” and “40 mg” script.

The 80 mg product is a size 0 (8 x 22 mm) blue opaque capsule with black “Lilly”, “2980” and “80 mg” script.

Both capsules are produced from the same blend formulation. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards with the exception of

excipients iron oxide black and Brilliant Blue FCF that complies with Commission Regulation (EU) No 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report. The compatibility of the active substance with the excipients has been adequately demonstrated.

The development of the finished product has been adequately described. Discussion about properties of active substance and excipients has been given. No incompatibilities have been identified. The influence of particle size and polymorphism of used active substances is discussed.

The development of the formulation composition is described. Bridging among the clinical and commercial presentations is explained. The clinical 40/80 mg formulation is identical to the commercial 40/80 mg formulation, with the exception of the printing on the commercial capsule. For bridging of clinical/commercial 40 mg and 80 mg formulations, based on the formulation similarity, a request of a waiver of in vivo bioequivalence demonstration for the 40 mg formulation was submitted. For the bridging of 40 mg and 20 mg clinical formulations, it was explained that the 40 mg clinical formulation uses the same blend as the 20 mg clinical formulation. The only difference between the two formulations is the capsule shell. Comparison of dissolution of 40 mg and 20 mg strength capsules (2 per vessel) were provided only for JP17 1st fluid (defined in the Japanese Pharmacopeia as pH 1.2 HCl with 0.2% NaCl) and pH 4.5 acetate buffer. Similarity of dissolution profile of 40 mg and 20 mg strength capsules (2 per vessel) was requested to be demonstrated at pH 6.8 and not only for JP17 1st fluid (defined in the Japanese Pharmacopeia as pH 1.2 HCl with 0.2% NaCl) and pH 4.5 acetate buffer (see GL GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The applicant further justified the absence of investigation of the similarity of dissolution profile of 40 mg and 20 mg strength capsules (2 per vessel) at pH 6.8. Bridging of 20 mg capsules to those used in earlier clinical studies was done using PK data (see PK assessment).

The manufacturing process development was sufficiently well documented. Some Quality-by-Design concepts and tools were used in the pharmaceutical development. CQAs are defined for the finished product and a Failure Mode Effect & Criticality Analysis (FMECA) is performed as a risk assessment for manufacturing process development. The FMECA summary presented is not fully in line with ICH Q9 (e.g., risk level of each parameter is not described in terms of severity, probability and detectability). However, since no regulatory flexibility or design spaces are claimed, it was considered acceptable detail.

A dissolution method has been developed for quality control (QC) during release and stability testing of the finished product. An aqueous medium is used and the pH has been evaluated in the physiological range (1-7.5). Apparatus 2 (paddles) at 75 rpm are selected for the dissolution method. Since paddle apparatus is used in the dissolution method, the stirring speed higher than 50 rpm (75 rpm) was requested to be justified. The rationale presented by the applicant supports that a paddle speed of 50 rpm provides equivalent dissolution behaviour to that of 75 rpm. Discriminatory power has been studied on batches with meaningful changes compared to the applied finished product (quantitative formulation and slightly modified process parameters). However, since the finished product contains an active substance which shows very rapid dissolution, it is not possible to detect any differences in the dissolution behaviour after meaningful changes. Hence the finished product specification limit for dissolution is set as per Ph. Eur. 2.9.3.

The primary packaging is a HDPE bottle. The material complies with Commission Regulation (EU) No 10/2011/EC and Ph. Eur. 3.1.3 Polyolefin.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: screening, blending, milling, blending, encapsulation and packaging. The process is considered to be a standard manufacturing process.

The in-process controls are adequate for this type of manufacturing process / pharmaceutical form. Results of process evaluation performed on a total of six batches: three for 40 mg strength and three 80 mg strength was provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Good Manufacturing Practice (GMP) process validation has been conducted for the 40 mg and 80 mg strength selpercatinib capsules at the commercial manufacturing site at commercial scale. A total of four batches are presented: one for 40 mg strength and three 80 mg strength. Process validation for the 40 mg strength is being performed concurrently while the 80 mg was validated prospectively.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: identity (HPLC-PDA), assay (HPLC), degradation products (HPLC), description (visual), uniformity of dosage units (Ph. Eur. / HPLC), dissolution (Ph. Eur. / HPLC), dye identity (titanium & iron test), Brilliant Blue FCF (UC) and microbiological testing (Ph. Eur.).

The finished product is released on the market based on the release specifications, through traditional final product release testing. The specifications comply with the general requirements of ICH Q6A guideline and the Ph. Eur.

The absence of a test for polymorphic form in the finished product specification was justified based on development and PK data.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

As part of the elemental impurities evaluation per ICH Q3D guidance, characterisation testing on primary stability finished product batches manufactured was performed using inductively-coupled plasma with mass spectrometry (ICP-MS). The data showed no Class 1 and Class 2A elemental impurities were present at any significant level and were well below (<30%) the ICH Q3D Option 2a limits. These data support that routine testing and specifications for Class 1 and Class 2A elemental impurities are not required for the finished product.

Batch analysis results are provided for three pilot scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Batch analysis results are also provided for batches used in clinical trials.

The applicant was requested to provide a risk evaluation concerning the presence of nitrosamine impurities in the product and applying the principles outlined in the notice "Information on nitrosamines for marketing authorisation holders (EMA/189634/2019)" at D120. A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been submitted. The identified root causes for presence of nitrosamines, listed in the Q&A on Information on nitrosamines for marketing authorisation holders (EMA/CHMP/409815/2020) have been considered. The information provided is deemed acceptable and confirms that there is no risk that nitrosamine impurities are present or can be formed.

Stability

Stability studies are currently being conducted on three batches of finished packaged in high density polyethylene (HDPE) bottles. These batches were manufactured by a process representative of the commercial process. Stability data for three batches of the 40 mg strength and three batches of the 80 mg strength are available up to 12 months for the long-term conditions of 30°C/65%RH and 25°C/60% RH and up to 6 months at accelerated storage

Supportive stability studies are also currently being conducted on batches of 20 mg and 80 mg selpercatinib capsules of the same formulation. A common blend is used for the 20 mg and 80 mg strengths. Up to 24 months of stability data are currently available for these batches and six months for all batches at the accelerated storage condition. Photostability testing has been performed on a single batch of each strength.

The results show no significant changes or trends on stability are observed.

In-use stability data were provided. According to EMA Q&A Part 2, storage without the protection of the immediate container is considered as a worst-case scenario and can in some instances be used to assess the need for an in-use shelf life. Since no relevant change is observed after 3 months of open dish storage, no in-use shelf life is necessary.

Based on available stability data, the proposed shelf-life of 2 years without special storage conditions as stated in the SmPC (section 6.3) are acceptable.

Post approval change management protocol(s)

Not applicable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture were provided.

GMO

Not applicable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

An initial major objection raised on the choice of starting materials was resolved by the applicant providing further justification and supporting data in line with ICH Q11. An initial major objection related to NORs/PARs and flexibility of active substance manufacturing process was resolved by defining set points for all relevant process parameters in the dossier.

The applicant addressed the potential risk of nitrosamine impurity formation in the active substance and finished product and it is confirmed that there is no risk that nitrosamine impurities are present or can be formed.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

All pivotal non-clinical safety studies were conducted in compliance with the Principles of Good Laboratory Practices (GLP), except the reproductive and developmental toxicity study: effect on embryo-foetal development (LOXO-292-TOX-009).

2.3.2. Pharmacology

Selpercatinib (LOXO-292) is an ATP-competitive small molecule inhibitor of the RET receptor tyrosine kinase. Several human malignancies have been identified with aberrant RET kinase activity. In this regard, it has been described as a potent oncogene, taking part in initiation and progression in multiple carcinomas and disorders, such as RET-mutant medullary thyroid cancer and RET fusion-positive non-small cell lung cancer. Selpercatinib has been proposed to inhibit both wild-type RET kinase and RET activating mutations (A883F, M918T, V804L and V804M).

Primary pharmacodynamic studies

In vitro

In vitro selpercatinib inhibited wild-type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3 with IC50 values ranging from 0.92 nM to 67.8 nM. (LOXO-292-PHARM-003, LOXO-292-PHARM-021; LOXO-292-PHARM-027).

Table 3. Inhibition of Wild-Type RET Kinase and RET Kinase Mutants by Selpercatinib at 1 mM ATP Concentration measured by HTRF KinEASE assay

Study number	**LOXO-292-PHARM-003: The kinase reaction was initiated when LOXO-292 was added to the reaction**			
Kinase Enzyme	ATP	IC50 (nM)	n	Fold vs.RET*
WT RET	1mM	17.3 ± 6.7	48	1
RET V804L	1mM	30.5 ± 4.2	30	1.8
RET V804M	1mM	36.7 ± 17.9	49	2.1
RET A883F	1mM	67.6 ± 32.2	21	3.9
RET M918T	1mM	28.7 ± 5.5	30	1.7
RET S891A	1mM	32.9 ± 10.3	21	1.9
Study number	**LOXO-292-PHARM-021 : LOXO-292 was incubated with the enzyme for 10 minutes at room temperature prior to the addition of ATP**			
Kinase Enzyme	ATP	IC50 (nM)	n	Fold vs.RET*
RET	1mM	2.79 ± 0.74	8	1
RET A764T	1mM	1.81 ± 0.42	8	0.6
RET L790F	1mM	0.92 ± 0.09	8	0.3
RET V804M	1mM	6.40 ± 0.75	8	2.3
RET M918T	1mM	1.50 ± 0.41	8	0.5
RET Δ(898-901)	1mM	0.97 ± 0.12	8	0.3
Study number	**LOXO-292-PHARM-027 : LOXO-292 was incubated with the enzyme for 10 minutes at room temperature prior to the addition of ATP**			
Kinase Enzyme	ATP	IC50 (nM)	n	Fold vs.RET*
RET G810S	1mM	294.88 ± 58.13	8	105.7**

Selpercatinib maintained significant activity against diverse RET mutations, including germline MTC activating mutations (A883F, M918T, S891A) and acquired resistance mutations to vandetanib and cabozantinib (V804L, V804M). (LOXO-292-PHARM-003, LOXO-292-PHARM-012, LOXO-292-PHARM-020; LOXO-292-PHARM-028).

Table 4. Activity of LOXO-292 on WT and muted RET and other kinases (LOXO-292-PHARM-003)

Enzyme	**ATP**	**IC50(nM) Mean±SD (n)**		
		Selpercatinib	**Vadetanib**	**cabozantinib**
wt RET	KM	0.4±0.1(24)	8.3±2.3(8)	6.8±1.1 (7)
Wt RET	1mM	17.3±6.7(48)	40.9±30.8(18)	149.1±52.2(16)
V804M RET	1mM	36.7±17.9(49)	≥9652.9±0(18)	2630.1±978.2(15)
V804L RET	1mM	30.5±4.2(30)		
G810R RET	1mM	680±273.7(23)	>10000±0 (17)	1559.9±708.7(15)
M918T RET	1mM	28.7±5.5(30)	ND	ND
A883F RET	1mM	67.6±32.2(21)	ND	ND
S891A RET	1mM	32.9±10.3(21)	ND	ND
Aurora A	No ATP	782±112.3(29)	>10000±0 (8)	1328.2±264.4(5)
Aurora B	No ATP	78.8±13.7(30)	≥9635.0±(6)	190.0±36.8(5)
FGFR1	Km	65.4 ±9.8(14)	264.4±96.2(6)	≥5139.9±0 (5)
FGFR2	Km	26.7±4.4(14)	84.5±45.6(5)	≥4530.0±0(5)
FGFR3	Km	53.8±14.2(14)	103.9±36.9(6)	≥4669.0±0(5)
FLT1	1mM	27.7±11.7(35)	39.8±20.4(21)	77.3±49.4(25)
FLT4	1mM	11.9±4.3(22)	ND	ND

In addition, selpercatinib had no significant antiproliferative effects in human cancer cell lines that do not express constitutively activated RET. Selpercatinib maintained significant selectivity for RET against non-kinase targets when tested in additional binding and cell-based assays. (LOXO-292-PHARM-016)

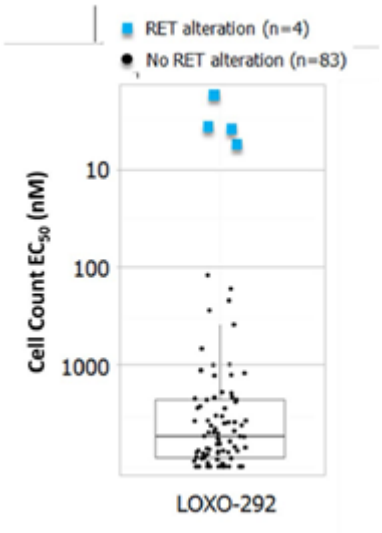


Figure 2. Selpercatinib selectively inhibits the proliferation of RET-altered cells (LOXO-292-PHARM-016)

In vivo

In mice implanted subcutaneously with NIH-3T3 cells engineered to express a constitutively active KIF5B-RET fusion protein, single oral doses of selpercatinib suppressed RET phosphorylation in tumours at single doses of 10 mg/kg and 30 mg/kg showed near complete inhibition of RET kinase activity (LOXO-292-PHARM-008). Selpercatinib administered 14 days caused dose-dependent inhibition of tumour growth of KIF5B-RET 3T3 tumours with 62%, 88%, 93% tumour regression when dosed at 10 mg/kg BID, 15 mg/kg BID and 30 mg/kg BID, respectively (LOXO-292-PHARM-006). Twice-daily oral dosing of selpercatinib caused inhibition of tumour growth in multiple RET-dependent tumour models including those harbouring a V804M gatekeeper mutation (KIF5B-RET-V804M NIH-3T3 and CR2545 CCDC6-RET-V804M) with 16%, 50% and 70% tumour regression when dosed at 10 mg/kg BID, 30 kg/kg BID and 100 mg/kg BID, respectively. The 100 mg/kg BID dosing schedule was not well tolerated as demonstrated by a mean body weight loss of 13.2% (LOXO-292-PHARM-007).

Selpercatinib also inhibited the growth of two different RET-dependent human cancer cell line mouse xenograft tumour models (TT human MTC cells harbouring an endogenous RET C634W substitution with 20% and 37% at 10 mg/kg BID and 30 mg/kg BID respectively and with 3% and 16 % in LC-2/ad human non-small cell lung cancer cells expressing a CCDC6-RET fusion (LOXO-292-PHARM-004(GLP)).

In Females BALB/c Nude mice implanted with CR2518 patient derived colorectal carcinoma xenograft (PDX) with a CCDC6-RET fusion protein with or without a V804M gatekeeper mutation, selpercatinib showed dose dependent inhibition of tumour growth with 108% and 113% tumour growth inhibition at doses of 10 mg/kg BID and 30 mg/kg BID, respectively (LOXO-292-PHARM-001(GLP)). In Female mice Athymic Nude-Foxn1 implanted with tumour model from CTG-0838 derived from Patient PDX with NSCLC that expresses a KIF5B-RET fusion protein orally (3 or 30mg/kg), selpercatinib caused dose-dependent inhibition of tumour growth with 82% and 106% tumour growth inhibition at day 25 for the 3 mg/kg BID and 30 mg/kg BID groups, respectively (LOXO-292-PHARM-017(GLP)).

Selpercatinib at orally 30 mg/kg BID inhibited the tumour growth of a RET fusion-positive PDX model implanted directly into the brain and demonstrated a significantly prolonged survival and was well tolerated throughout the 84 days of dosing (LOXO-292-PHARM-013).

Secondary pharmacodynamic studies

Selpercatinib was more selective for RET over 98% of 329 non-RET kinases including VEGFR2 (Eurofins KinaseProfiler) tested in a large in vitro kinase activity screen. Among the remaining 2% of kinases, Selpercatinib inhibited the kinase activities of RET, FLT1 (VEGFR1), and FLT4 (VEGFR3), in similarly executed assays containing 1 mM ATP, with IC50 values of 17.3 nM, 27.7 nM and 11.9 nM, respectively (LOXO-292-pharm-003).

However, in more physiologically relevant cell-based assays, selpercatinib inhibited FLT4 with an IC50 value of 33 nM, which is ~8-10 fold higher than the IC50 value for RET in cells (3.3 nM - 4 nM). (LOXO-292-pharm-009)

A significant inhibition ($\geqslant$ 50%) was observed for two targets: the 5-HT (serotonin) transporter (70.2% inhibition of antagonist radioligand) and a2c(h) (51.7% inhibition of antagonist radioligand). There was no other significant inhibitory activity in any of the other assays. (LOXO-292-PHARM-002)

Safety pharmacology programme

For CNS and CV, safety pharmacology was investigated in the context of repeated-dose toxicity studies in rat and minipig with individual safety pharmacology endpoints, with additional dedicated safety pharmacology studies for CV. Respiratory function was investigated in a dedicated study.

Cardiac function

The cardiac safety of selpercatinib was evaluated in several in vitro assays, including in vitro assays for hERG activity, safety pharmacology studies using conscious telemetry-instrumented in only males minipigs given selpercatinib orally, and by monitoring ECGs in repeated-dose oral toxicity studies 28 and 91 days in duration in males and females minipigs.

In Vitro

Selpercatinib had an IC50 value of 1.1 µM in the GLP hERG assay, which is approximately 7-fold higher than the maximum unbound concentration (geometric mean Cmax (unbound) = 153 nM) at the clinical dose of 160 mg BID (LOXO-292-SPHARM-003). In ion channel-blocking assays, selpercatinib only block hERG with a minimal to no effects on other cardiac channels (LOXO-292-SPHARM-001).

In vivo

The dose of 12 mg/kg was selected for the safety pharmacology cardiovascular study based on results from the 14-day minipig study in which the 25 mg/kg dose was not tolerated.

No abnormal ECG waveforms, arrhythmias or quantitative effects on ECG and hemodynamic data occurred after single doses up to 12 mg/kg when given orally to conscious telemetry-instrumented males minipigs. At this dose, the Cmax corresponded to 909 ng/mL after a single dose which is approximately 0.3 times the human geometric mean maximum concentration (Cmax = 2980 ng/mL) at the clinical dose of 160 mg BID. (LOXO-292-SPHARM-002)

In the 28-day males and females minipigs repeated-dose toxicity study, there were no ECG changes at doses up to 12 mg/kg which corresponded to a Cmax of 1120 ng/mL on Day 22. (LOXO-292-TOX-002)

In the 91-day males and females minipigs repeated-dose toxicity study, females given 5 mg/kg/day were noted with a slight significant increase in QTc prolongation on Day 88 of the dosing phase. This prolongation was approximately 12% and 7 % relative to controls and pre-dose values, respectively. The dose of 5 mg/kg/day corresponded to a mean Cmax of 565 ng/mL for females on Day 91 which is

approximately 0.2 times the human geometric mean maximum concentration (Cmax = 2980 ng/mL) at the clinical dose of 160 mg BID. (LOXO-292-TOX-012)

CNS

The Effects of selpercatinib on the CNS were not evaluated in a dedicated safety pharmacology study but as part of the GLP 28-day repeated-dose oral toxicity study in SD rats (LOXO-292-TOX-001). Functional observational battery and locomotor activity were conducted during predose, dosing and recovery phase.

On day 23 of dosing-decrease in the incidence of low locomotor activity in arena in the high-dose, a decreased Mean forelimb grip strength in males given 75/45 mg/kg/day that was reversible after the recovery period and decrease in number of basic movements and X + Y ambulation in high-dose males on day 23.The doses were established as the severely toxic doses in 10% of animals (STD10) in the GLP 28-day repeated-dose study.

Respiratory function

Effects on respiratory function (tidal volume, respiration rate, and minute volume) were also investigated in a stand-alone GLP respiratory function study using the head-out plethysmography in male SD rats. (LOXO-292-SPHARM-004)

The single oral gavage dose of up to 45 mg/kg to male Crl:CD(SD) rats caused no general clinical observations or effects on respiratory function up to 24 hours post dose. The dose of 45 mg/kg of selpercatinib is considered to be the NOEL with respect to respiratory function in the rat.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions study was submitted.

2.3.3. Pharmacokinetics

The pharmacokinetics and metabolism of selpercatinib have been examined through a series of in vitro and in vivo studies, including toxicokinetic studies. Selpercatinib has been given orally and intravenously to mice, rats, dogs, and minipigs. Oral pharmacokinetics have also been determined in the rabbit and monkey.

In vitro, selpercatinib has a high protein binding in human plasma (97%), in mouse (98%) and in rat (97%), with a lower bound in dogs (90%) and minipigs (88%).

Absorption

Selpercatinib has a good exposure after oral administration in the mouse, rat, rabbit, dog, monkey, and minipig, and thus demonstrates at least moderate intestinal absorption.

In rats, there was no difference in bioavailability between solution and suspension formulations.

Data on the multiple-dose pharmacokinetic properties of selpercatinib were also obtained from the repeat-dose toxicity studies in the rat (4-, 14-, 28-, and 91-day) and minipig (14-, 28-, and 91-day) GLP studies. Sex differences in exposure in rodents was shown in rats studies with generally a greater exposure in males but with no difference between repeated doses and single dose across all studies.

Exposure, as assessed by mean Cmax and AUC0-24 values, increased with the increase in dose level in all three minipig studies. A small degree of accumulation (approximately 1.5-fold) was noted between the first and last day of dosing.

A pH-dependent solubility of selpercatinib where seen in dogs with a greater exposure when stomach pH was acidified with pentagastrin in comparison with a neutralized stomach pH.

Distribution

Selpercatinib distributes into tissues with a volume of distribution ranging from 1.62 to 5.36 L/kg in the mouse, rat, dog, and minipig.

Selpercatinib distribute into a large number of tissues with a predominant in meninges and tissues containing ocular melanin and integumentary melanin with at last sampling time of 672 hours postdose, persisted radioactivity in ocular or pigmented tissues (uveal tract, vitreous humor, eyes, pigmented skin and meninges).

Following a 3-, 100-, or 300-mg/kg oral dose of selpercatinib to male CD-1 mice, the brain/plasma ratio of selpercatinib was approximately 0.03, 0.05, and 0.07, respectively. These data suggest limited penetration of selpercatinib into the CNS in mice, however pharmacodynamics studies suggest anti-tumour activity of selpercatinib in the brain of mice.

In mouse, rat, and human blood, the blood-to-plasma ratios were less than one, suggesting that a greater portion of the compound resides in the plasma compartment than in blood cells, whereas the blood-to-plasma ratio of selpercatinib in beagle dog was approximately one, suggesting that a similar portion of the compound resides in the blood and plasma compartments.

Metabolism

Selpercatinib was stable during incubation with human whole blood, but metabolized by microsomal fractions and hepatocytes from mice, rats, dogs, minipigs, and humans.

The predicted Selpercatinib human clearance of 13 and 5 mL/min/kg, based on hepatic microsomes and hepatocytes, corresponds to 64% and 25% of liver blood flow, respectively.

Based on semi-quantitative mass spectrometer ion current, unchanged selpercatinib was the major component in plasma of rats, minipigs and human cancer patients.

Six metabolites were identified in human plasma: two oxidized metabolites (M2 and M5), an O-desmethyl metabolite (M3), an N-dealkylated metabolite (M4), a secondary di-oxidized metabolite (M7), and an O-dealkylated glucuronide conjugate (M6). M2 was determined to be an N-oxide of selpercatinib at the N-6 nitrogen of the piperazine moiety, and structure confirmed by lack of hydrogen-deuterium exchange, reduction by $TiCl_3$, and co-elution with a synthetic selpercatinib N6-oxide standard.

A human study with [14C]-selpercatinib showed that none of the metabolites of selpercatinib accounted for more than 10% of total drug-related material in plasma.

Excretion

In minipigs given an IV dose of selpercatinib, urine collected through 48 hours after dosing contained 2.63% of the administered dose.

Pharmacokinetic drug interactions

Selpercatinib was incubated with cloned, expressed human CYP450 enzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 Only CYP3A4 was able to metabolize Selpercatinib. These data indicated that CYP3A4 is responsible for the metabolism of Selpercatinib (LOXO-292-DMPK-017).

Selpercatinib showed some induction of CYP2B6 and CYP3A4 at higher concentrations (LOXO-292-DMPK-018)

Selpercatinib showed weak inhibition of CYP2C8 (IC50 of 3.4 µM) and time-dependent inhibition of CYP3A4 (*LOXO-292-DMPK-010)*.

In vitro, Selpercatinib inhibits the transporter MATE1 with an IC50 of 0.666 µM (LOXO-292-DMPK-035). No other drug transporters were inhibited significantly at a clinically relevant unbound plasma geometric mean Cmax of 153 nM.

Table 5: **Inhibition of Drug Transporters by Selpercatinib**

Transporter	IC_{50} (µM)	$I_{max,u}$ (unbound C_{max}, µM)	$I_{max,u}/IC_{50}$
P-gp (quinidine substrate) [a]	5.4	0.153	0.03
P-gp (digoxin substrate, MDCK assay) [b]	10.7	0.153	0.01
P-gp (digoxin substrate, vesicle assay) [b]	45.0	0.153	< 0.01
BCRP (MDCK cell assay) [c]	5.10	0.153	0.03
BCRP (vesicle assay) [c]	22.3	0.153	< 0.01
OATP1B1 [c]	18.0	0.153	< 0.01
OATP1B3 [c]	8.32	0.153	0.02
BSEP [c]	> 30	0.153	< 0.01
OAT1 [c]	> 30	0.153	< 0.01
OAT3 [c]	> 30	0.153	< 0.01
OCT1 [c]	> 30	0.153	< 0.01
OCT2 [c]	12.9	0.153	0.01
MATE1 [c]	0.666	0.153	0.23
MATE2K [c]	3.42	0.153	0.04

[a] LOXO-292-DMPK-020
[b] LOXO-292-DMPK-055
[c] LOXO-292-DMPK-035

2.3.4. Toxicology

Selpercatinib showed toxicity in both rats and minipigs with large target organs and tissues. Finding were in the haemtopoietic system, lymphoid system, gastrointestinal system (tongue in rat only), pancreas, skeletal system (epiphyseal growth plate of femur/sternum) and reproductive system. The toxic effects noted with selpercatinib share similarities to toxicities described in the literature for multi-kinase inhibitors with anti-RET activity.

Selpercatinib did not demonstrate phototoxic potential in the in vitro neutral red uptake assay in BALB/c 3T3 mouse fibroblasts.

Single dose toxicity

Acute toxicity data were obtained from two in vivo micronucleus assays in rats.

A first single dose effect was examined in SD male and female rats with oral single dose of Selpercatinib 250, 500, 1000 and 2000 mg/kg. A second single dose effect examined in SD male rats given a single oral dose of 37.5, 75, 150, 300 or 500 mg/kg of selpercatinib. Toxicity parameters measured were clinical signs and body weightsNo mortality occurred at any dose level Piloerection and body weight loss were observed in rats given with selpercatinib at ⩾ 150 mg/Kg.

Repeat dose toxicity

In rat

Study ID GLP	Species Test system	Majors findings
4-day with TK Non –pivotal study LOXO-RET-TOX-006 Non GLP Batch	Rat Sprague Dawley Males and females 4/group /sex Oral Gavage Males: 10, 30, and 100mg/kg/day Females: 30, 100 and 300mg/kg/day Duration: 4 days	Thinness, hunched posture and erected fur in females at 300 mg/kg/day only from ~ Day 4 through recovery (Day 9). Males at 100 mg/kg/day (61 % less than controls) had decreased body weight gain from Day 4 through 7. Females at 300 mg/kg/day had body weight loss from Days 4 to 7. Decrease in females given 300 mg/kg/day from Days 2 to 8 (78%, less than controls on Day 4). Decrease in males given 100 mg/kg/day between Days 2 to 6 (range of 9 to 25% less than controls).
14-days with TK Non pivotal study LOXO-RET-TOX-007 Non GLP Batch	Rat Sprague Dawley Males and Females 5/group /sex Oral Gavage Males: 10, 30 and 100mg/kg/day Females: 20, 60 and 180 Duration: 14 days	**Clinical Observations**: Thinness, ungroomed fur, and piloerections in males at 100 mg/kg/day Decrease in bodyweight gain in males at 100 mg/kg/day up to Day 11 (67 % less than controls on Day 11). Bodyweight loss from Days 11-14 in males given 100 mg/kg/day. At ≥10 mg/kg/day and ≥20 mg/kg/day in males and females, respectively, dose-dependent mild to moderate ↓in reticulocytes. At 100 mg/kg/day and in one male at 30 mg/kg/day minimal ↑in red blood cell mass indices (haemoglobin, red blood cell count and haematocrit). At 10 mg/kg/day in males a non-dose dependent minimal to mild ↑in neutrophils and monocytes. At 100 mg/kg/day in males and ≥60 mg/kg/day in females mildly ↓ lymphocytes. At ≥10 mg/kg/day in males and in one female at 60 mg/kg/day a dose-dependent minimal to mild ↓ in platelets **Clinical Chemistry (Day 15):** At ≥ 30 mg/kg/day in males: ↑in triglycerides, alanine aminotransferase, aspartate aminotransferase, and phosphorus and ↓in albumin. at 100 mg/kg/day Minimal ↑in cholesterol and total bilirubin in males. At ≥ 60 mg/kg/day Minimal to mild ↑in alkaline phosphatase and phosphorus and ↓in albumin in females. Increase in cholesterol, triglycerides, alanine aminotransferase and aspartate aminotransferase in females at 180 mg/kg/day. **Organ weights:** ↓in thymus and liver (absolute and relative) in males at 100 mg/kg/day. **Microscopic findings** at ≥ 30 mg/kg/day for males and at 180 mg/kg/day for females**:** Mild to severe physeal dysplasia in femur and/or sternum. At 100 and ≥ 60 mg/kg/day of males and females, respectively hypocellularity of bone marrow. Erythroid and myeloid lineage affected. The incidence and severity of physeal dysplasia, bone marrow hypocellularity and gastric mineralisation were considered adverse at ≥ 30 mg/kg/day (males) and at ≥ 60 mg/kg/day (females). (NOAEL) was considered to be 10 mg/kg/day for males (on Day 14, Cmax: 2720 ng/mL and AUC(0-t): 32400 hr*ng/mL) and 20 mg/kg/day for females (on Day 14, Cmax: 4870 ng/mL and AUC(0-t): 12200 hr*ng/mL).
28-days with TK Pivotal study LOXO-292-TOX-001 GLP	Rat Sprague Dawley Males and Females 15 /group /sex Oral Gavage once daily Males: 0, 5, 20 or 75/45mg/kg/day Females: 0, 15, 50, or 150/120	Based on dose, males were more sensitive than females but Clinical signs at the high dose in both sexes were adverse. Males had lower body weight and high dose animals had lower body weight gain; food consumption was ↓ in both sexes. During the recovery phase, malocclusion contributed to body weight loss, and powdered meal was fed to high dose animals from Day 9 of recovery. Effects on body weight did not fully reverse and were considered adverse. At the high doses, toxicity targets included: effects on bone marrow, liver (no microscopic correlate), physis, multiple tissues (mineralisation), tongue, pancreas, lung, Brunner's gland and incisor teeth. At the high doses of 20 mg/kg/day and 75 mg/kg/day for males and females, respectively, Selpercatinib-related clinical observations included non-reversible teeth abnormalities (malocclusion, white incisor teeth, and missing teeth) and thinning haircoat on the head and/or shoulders.

	mg Duration: 28 days with 28 days recovery phase	In males administered 2.0 mg/kg/day thinning haircoat on the head was also noted.
91-days with TK and male and females exploration of **LOXO-282-TOX-011**	Rat Sprague Dawley Males and Females 15 /group /sex Oral Gavage once daily Males: 0, 2, 7.5 or 20 mg/kg/day Females: 0, 7.5, 25 or 75 mg/kg/day Duration: 91 days with 4 weeks recovery phase	At the terminal sacrifice, key Selpercatinib-related microscopic findings occurred in the testis, epididymis, and vagina. In the bone marrow (femur and sternum) and lung: in males at 20 mg/kg/day and females at 75 mg/kg/day↓ bone marrow cellularity (minimal severity) with relative ↓ in the numbers of haemtopoietic cells (erythroid and myeloid cells), with an ↑ prominence of adipocytes in the bone marrow. Correlated in male with lower reticulocyte count clinically in males at 20 mg/kg/day. At 20 mg/kg/day and females at 75 mg/kg/day ↑incidence of alveolar macrophage infiltrates in the lung. The testicular change, tubular degeneration/atrophy in males administered ≥7.5 mg/kg/day, correlated with macroscopic findings of small or soft testis and decreased testis weights in males administered 20 mg/kg/day. Selpercatinib-related findings in the epididymis included luminal cell debris and reduced luminal sperm in males administered 20 mg/kg/day, which were considered secondary to microscopic findings in the testis at this dose. Selpercatinib-related findings in the vagina of terminal sacrifice females administered ≥25 mg/kg/day included increased mucification of the vaginal epithelium and an altered (unstageable) oestrous cycle. In the bone marrow (femur and sternum), a microscopic finding of decreased cellularity occurred in males administered 20 mg/kg/day and females administered 75 mg/kg/day and may have correlated with the haemtology finding of lower reticulocyte count in males administered 20 mg/kg/day. Finding in the lung of males administered 20 mg/kg/day and females administered 75 mg/kg/day was an increased incidence of alveolar macrophage infiltrates. At the recovery sacrifice, testis and epididymis findings persisted in males administered ≥7.5 mg/kg/day. Degeneration/atrophy in the testis of recovery males administered 20 mg/kg/day was generally more severe than in males affectedd at the terminal sacrifice and correlated with macroscopic findings of soft testis and decreased testis weights in recovery sacrifice males administered that dose level. Epididymis findings included luminal cell debris in males administered ≥7.5 mg/kg/day and reduced luminal sperm in males administered 20 mg/kg/day. The microscopic findings in the epididymis of males administered 20 mg/kg/day correlated with decreased epididymis weight and was considered secondary to the testis changes. All other Selpercatinib-related microscopic findings noted in terminal sacrifice animals had recovered.

In Göttingen Minipigs

<u>14-day daily repeat dose oral toxicity and toxicokinetic study of selpercatinib in Göttingen minipigs (study LOXO-RET-TOX-008, non-GLP)</u>

The study investigated 3 minipigs per sex/group at the doses of 0, 5, 25 or 65 mg/kg/day for a duration of 14 days. Selpercatinib was administered by oral gavage.

Assessment of toxicity was based on mortality, clinical observations, food consumption, and clinical and anatomic pathology on selected organs. Blood samples were collected for toxicokinetic evaluations on Day 1 and 14.

Oral administration of 65 mg/kg/day of Selpercatinib to Göttingen minipigs was poorly tolerated and resulted in the unscheduled sacrifice of all six animals administered this dose. The most prominent microscopic findings included decreased cellularity of the bone marrow, with secondary septicaemia, atrophy of the ovary, and epithelial blunting/fusion or atrophy in some segments of the small and large intestines.

<u>28-day oral gavage toxicity in Göttingen minipigs followed by a 28-day recovery period (study LOXO-292-TOX-002, GLP)</u>

The study investigated 6 minipigs per sex/group at the doses of 0, 2, 5, 12 mg/kg/day for a duration of 28 days followed by 28 days recovery phase.

Assessment of toxicity was based on mortality, clinical observations, body weights, ophthalmic observations, electrocardiographic (ECG) measurements, and clinical and anatomic pathology.

Selpercatinib was well tolerated when administered to Göttingen Minipigs by oral gavage for 28 days at a dose level of 2, 5, or 12 mg/kg/day. No test article-related effects on clinical observations, body weight, or food consumption were noted.

No selpercatinib-related effects were observed on clinical observations, body weight, ophthalmic examinations, ECG evaluations, organ weights, or macroscopic examinations. Based on the lack of adverse findings, the dose of 12 mg/kg/day was the no observable adverse effect level (NOAEL).

91-Day Oral Gavage Toxicity in Göttingen Minipigs Followed by a 28-Day Recovery Period (study LOXO-292-TOX-012, GLP)

The study investigated 6 minipigs per sex/group at the doses of 0, 2, 5, 12 mg/kg/day for a duration of 91 days followed by 28 days recovery phase. Selpercatinib was administered by oral gavage.

Three males and four females administered 15 mg/kg/day were sacrificed in a moribund condition on Day 27 (males) or 26 (females) of the dosing phase. These unscheduled sacrifices were considered selpercatinib-related.

Animals sacrificed in a moribund condition on Day 26 or 27 had one or more Selpercatinib-related clinical pathology changes consistent with an inflammatory response, which involved the gastrointestinal tract, physeal changes, dehydration and general debilitation. Changes correlated with microscopic evidence of inflammation in the non-glandular mucosa of the stomach and esophagus and increased thickness of the physis.

Selpercatinib-related microscopic findings in unscheduled sacrifice animals administered 15 mg/kg/day were not specifically associated with moribund condition:

-changes in the femur (minimal to marked increased thickness of the physis),

-testis (slight tubular degeneration/atrophy), epididymis (minimal luminal cellular debris),

-ovary (marked decrease in numbers of corpora lutea and the presence of corpora luteal cysts),

-esophagus (minimal to moderate mucosal atrophy, slight mucosal degeneration/necrosis,

-neutrophilic inflammation, and/or moderate ulcer/erosion),

-tongue (minimal to slight mucosal atrophy)).

A slight increase in QTc prolongation was noted on Day 88 of the dosing phase in females administered 5 mg/kg/day compared with the time-matched percentage change for the control group and predose values (approximately 12% and 7%, respectively).

Genotoxicity

Conventional studies of genotoxicity (Ames test in Salmonella typhimurium and Escherichia coli reverse mutation assay, *in vitro* micronucleus assay in human peripheral blood lymphocytes and bone marrow micronucleus assay following oral administration to rats) were conducted with selpercatinib. Selpercatinib is not genotoxic at therapeutic doses. Selpercatinib did not cause mutations in a bacterial mutagenicity assay. In an in vivo micronucleus assay in rats, selpercatinib was positive at concentrations >7 times the Cmax at the human dose of 160 mg twice daily. In an *in vitro*

micronucleus assay in human peripheral blood lymphocytes, an equivocal response was observed at a concentration approximately 485 times the Cmax at the human dose.

Carcinogenicity

No carcinogenicity studies were conducted.

Reproduction Toxicity

The applicant has conducted studies in rats and minipigs to assess the effect of selpercatinib on male and female fertility. In the female fertility study (LOXO-292-TOX-023), adverse findings on oestrous cycles and embryonic survival were reported at the high dose level of 75 mg/kg inducing exposure levels within the clinical range. A reduction in the number of oestrous cycles were already reported in repeat-dose toxicity studies but did not impact on mating performance or fertility. However, embryolethality was reported with half of the females having 100% nonviable embryos at 75 mg/kg. This is in line with the results of the dose-range finding EFD study (increased post implantation loss due to increased early resorptions from the low dose of 50 mg/kg/day). Overall, a concern for female fertility is confirmed considering notably the findings observed at subclinical exposure levels (0.07 to 0.3 times the clinical exposure at the recommended human dose) in minipig studies (ovarian atrophy, decreased corpora lutea, corpora luteal cysts). In male rats (LOXO-292-TOX-025), germ cell depletion and spermatid retention were seen from the low dose of 3 mg/kg/day inducing subclinical exposure to the test-article (x0.2 clinical AUC). Decreased testis weight (likely due to germ cell depletion), altered sperm parameters (morphology, motility), and epididymal findings were also observed at the high dose level of 30 mg/kg/day (x2 clinical AUC).

In a dose-range finding embryo-foetal development study (LOXO-292-TOX-009) conducted in rats at doses of 50, 100 and 200 mg/kg/day, selpercatinib induced developmental toxicity embryolethality (early resorptions) at all dose levels. At 50 mg/kg/day, only 3 foetuses from two litters could be evaluated; they were found to be affected by treatment-related and adverse malformations (local foetal oedema of neck and thorax, small snout, short tail). Hence, a foetal developmental NOAEL could not be determined. Exposure level at the low dose level were in the clinical range (animal-to-human exposure ratio of 1.5).

Toxicokinetic data

Exposure comparisons in the animals and humans (AUC0-24, Cmax) are shown in Table 35. The total plasma geometric mean Cmax of 2980 ng/mL and AUC of 51600 ng*h/mL for selpercatinib in adult patients at steady state following 160 mg BID (198 mg/m2/day) was used for exposure margin calculations.

AUC values at the STD 10 in the rat 28-day study corresponded to approximately 3-5 times the human geometric mean AUC at the recommended clinical dose. The HNSTD in the 91-day study in rat was 20 mg/kg/day (120 mg/m2/day) and 75 mg/kg/day (450 mg/m2/day) for males and females, respectively and corresponded to approximately 2 to 3 times the human geometric mean AUC at the recommended clinical dose. The NOAEL for EFD in the rat (100 mg/kg/day or 600 mg/m2/day) corresponded to approximately 4 times the human geometric mean AUC at the recommended clinical dose. In the 28-day study in minipig, the NOAEL was 12 mg/kg/day (420 mg/m2/day) and exposure at this dose corresponded to approximately 0.4 times the human geometric mean AUC at the recommended clinical dose.

In the 91-day study in minipig, the HNSTD and NOAEL was 5 mg/kg/day (175 mg/m2/day) and exposure at this dose corresponded to approximately 0.2 to 0.3 times the human geometric mean AUC at the recommended clinical dose.

Table 6. Comparative Systemic Exposure to Selpercatinib after Oral Administration of Selpercatinib to Adult Rats, Pregnant Rats, Göttingen Minipigs, and Humans

Species	selpercatinib (mg/kg/day)	Systemic (Plasma) Exposure						
			Type of Study	C_{max}[1] (ng/mL)	C_{max} Exposure Ratio[1,2]	AUC_{0-24}[1] (ng*h/mL)	AUC Exposure Ratio[1,3]	Report No.
Rat - Repeat Dose Studies								
Rat, male	20 (120 mg/m²/day)	NOAEL	28-day repeat-dose study	4450	2	50800	1	LOXO-292-TOX-001
Rat, female	50 (300 mg/m²/day)	NOAEL		8380	3	39100	0.8	
Rat, male	45 (270 mg/m²/day)	STD 10		11700	4	151000	3	
Rat, female	120 (720 mg/m²/day)	STD 10		19100	6	260000	5	
Rat, male	7.5 (45 mg/m²/day)	NOAEL	91-day repeat-dose study	1490	0.5	18500	0.4	LOXO-292-TOX-011
Rat, female	25 (150 mg/m²/day)	NOAEL		10700	4	50400	1	
Rat, male	20 (120 mg/m²/day)	HNSTD		6780	2	80400	2	
Rat, female	75 (450 mg/m²/day)	HNSTD		15700	5	149000	3	
Minipig - Repeat Dose Studies								
Minipig, male and female	12 (420 mg/m²/day)	NOAEL	28-day repeat-dose study	1120	0.4	23200	0.4	LOXO-292-TOX-002
Minipig male	5 (175 mg/m²/day)	HNSTD	91-day repeat-dose study	712	0.2	13200	0.3	LOXO-292-TOX-012
Minipig, female	5 (175 mg/m²/day)	NOAEL		565	0.2	11900	0.2	
Rat – In vivo Micronucleus Assay								
Rat, male	37.5 (225 mg/m²/day)	Negative	In vivo micronucleus assay	9210	3	112000	2	LOXO-292-TOX-021
	75 (450 mg/m²/day)	Negative		15200	5	245000	5	
	150 (900 mg/m²/day)	Negative		21000	7	481000	9	
	300 (1800 mg/m²/day)	Positive		34000	11	1080000	21	
	500 (3000 mg/m²/day)	Positive		34300	12	1190000	23	
Rat - Embryo Fetal Development								
Rat, pregnant female	100 (600 mg/m²/day)	NOAEL for maternal toxicity	Embryo-fetal development	14600	5	185000	4	LOXO-292-TOX-009
Human								
Human	160 mg BID (198 mg/m²/day)	N/A	N/A	2980[4]	N/A	51600[4]	N/A	LOXO-RET-17001

[1] AUC_{0-24} and C_{max} values indicate mean total plasma concentrations, unless noted otherwise.

[2] The C_{max} exposure ratio was calculated as $C_{max,animal}/C_{max,human}$ following repeated dosing.

[3] The AUC exposure ratio was calculated as $AUC_{0-24,animal}/AUC_{0-24,human}$ following repeated dosing.

[4] Geometric mean $C_{max,human}$ and $AUC_{0-24,human}$ were the steady-state values (Day 8) from Clinical Study LOXO-RET-17001 where adult patients (410 patients) received 160 mg BID (visit cutoff 17 June-2019).

NA = not applicable

Local Tolerance

No dedicated local tolerance testing was conducted. The gastrointestinal tract was evaluated in all repeat-dose toxicology studies in Sprague-Dawley rats and minipigs.

Other toxicity studies

Juvenile studies

Preliminary, non GLP- compliant studies were conducted in juvenile rats aged 7 days at initiation of treatment (a single dose (LOXO-292-TOX-017) and two dose-range finding toxicity studies (LOXO-292-TOX-019, LOXO-292-TOX-022).

Phototoxicity assay

Neutral Red Update Phototoxicity Assay of LOXO-292 in BALB/c 3T3 Mouse Fibroblasts An in vitro neutral red uptake phototoxicity assay was conducted in BALB/c 3T3 mouse fibroblasts with selpercatinib. Selpercatinib was not found to be phototoxic in this study.

However in the distribution study on male Long Evans pigmented rat, selpercatinib shows a high distribution into tissues containing ocular melanin and integumentary melanin and in meninges with at last sampling time of 672 hours postdose, persisted radioactivity in ocular or pigmented tissues (uveal tract, vitreous humor, eyes, meninges, and pigmented skin).

2.3.5. Ecotoxicity/environmental risk assessment

Table 7. Summary of Main Study Results

Substance (INN/Invented Name): Selpercatinib / Retsevmo
CAS-number (if available): 2152628-33-4

PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Kow values of 1.3, 3,08 and 3.45 at pH 5, pH 7 and pH 9	Potential PBT: no bioaccumulation potential
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	of 1.3, 3,08 and 3.45 at pH 5, pH 7 and pH 9	not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not 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)	0.0099	µg/L	> 0.01 threshold N
Phase II Physical-chemical properties and fate			
Not required			
Phase IIa Effect studies			
Not required			

2.3.6. Discussion on non-clinical aspects

Selpercatinb inhibits RET, RET fusions, and multiple RET mutants with a good potency and selectivity. In vitro selpercatinib inhibited the wild type RET kinases. 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 arbouring 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 (see section 5.3 of the SmPC).

The safety pharmacology studies using conscious telemetry-instrumented animals was only conducted in male minipigs. The dose of 12 mg/kg did not show a cardiac toxic effect. However, in the 91-day minipig repeated-dose study, females administered the mid dose of 5 mg/kg/day exhibited a slight increase in QTc interval of approximately 12% and 7 %, relative to controls and pre dose values, respectively. In addition, considering the risk of QT interval prolongation based on clinical experience with Selpercatinib and clinical and non-clinical finding with multi-kinase inhibitors with anti-RET activity (vandetanib, sunitinib, and lenvatinib), a warning has been included in section 4.4 of the SmPC). Significant inhibition (IC50 ≥ 50%) was observed for the 5-HT transporter (70.2% antagonist radioligand) and a2c(h) (51.7% antagonist radioligand). The concentration of 1 µM is approximately 7-fold higher than the maximum unbound plasma geometric concentration (Cmax(unbound) = 153 nM) at the clinical dose of 160 mg BID. No other receptors or enzymes were inhibited ≥ 50% (see section 5.3 of the SmPC). Dependence to Selpercatinib was considered not likely and therefore dependence studies were not considered relevant.

Selpercatinib was orally bioavailable in the mouse, rat, rabbit, dog, monkey, and minipig, and thus demonstrates at least moderate intestinal absorption. The physicochemical properties of selpercatinib, along with *in vitro* data and *in vivo* data in six preclinical species, suggest that selpercatinib is likely to be well absorbed after its oral administration. A pH-dependent solubility of selpercatinib suggest that selpercatinib exposure could be lower in patients treated with proton pump inhibitors and other antacids; and a reduction in exposure was demonstrated in humans (see section 4.5 of the SmPC).

Selpercatinib shows a high distribution into tissues containing ocular melanin and integumentary melanin and (uveal tract, vitreous humour, eyes, meninges, and pigmented skin).

The rates of metabolism suggested that selpercatinib will have moderate clearance in humans. Except the metabolite M1 (glutathione conjugate), the predominant human metabolites detected *in vitro* were the same detected with rat and/or minipig microsomes and hepatocytes). M2, M3, and M4 and M5 were present in the plasma of rats and minipigs dosed orally with selpercatinib.

Six metabolites were identified in human plasma: two oxidized metabolites (M2 and M5), an O-desmethyl metabolite (M3), an N-dealkylated metabolite (M4), a secondary di-oxidized metabolite (M7), and an O-dealkylated glucuronide conjugate (M6).

CYP3A4 appeared to contribute significantly to the clearance of Selpercatinib, there was the potential for co-administered inhibitors and inducers of CYP3A4 to affect the PK of Selpercatinib.

Overall, the pharmacokinetic data for selpercatinib indicate it is well absorbed after oral administration and has the appropriate characteristics to enable its pharmacological and toxicological evaluation.

Repeat-dose studies were conducted in rats and minipigs to characterize toxicity. Target organs of toxicity common to the rat and minipig were haemtopoietic system, lymphoid tissues, tongue, pancreas, epiphyseal growth plate, and male reproductive tissues. In general, toxicities in these organs were reversible; the exception was the testicular toxicity. Reversible toxicity was observed in the ovaries and gastrointestinal tract in minipigs only; at high doses, gastrointestinal toxicity caused morbidity at exposures in minipigs that were generally lower than exposures determined in humans at the recommended dose. In one minipig study, females exhibited a slight, reversible increase in QTc prolongation of approximately 12% compared to controls and 7 % compared to pre-dose values. Target organs of toxicity observed only in rats were incisor tooth, liver, vagina, lungs, Brunner's gland, and multi-tissue mineralisation associated with hyperphosphatemia. These toxicities only occurring in these organs in rats were reversible (see section 5.3 of the SmPC).

Selpercatinib was considered non genotoxic based on the negative result of GLP bacterial mutation assay and the in vitro micronucleus assay in HPBL while in an *in vivo* micronucleus assay in rats, selpercatinib was positive at concentrations >7 times the C_{max} at the human dose of 160 mg twice daily. As with other RTK inhibitors, the bone marrow is a target organ for selpercatinib. Those findings are reflected in section 5.3 of the SmPC.

This initial MAA follows the guidance of ICH S9 which states that carcinogenicity studies are not scientifically warranted to support marketing for therapeutics intended to treat patients with advanced cancer. However, as MTC has a high prevalence of RET mutations but is often a slow growing tumour, the applicant is recommended to conduct carcinogenicity studies in rats and in RasH2 transgenic mice. The live phase of the rat study is expected to complete in May 2023, with a final report available in April 2024. The live phase of the mouse study is expected to complete in November of 2021, with a final report available in October of 2022.

The applicant has submitted studies in rats to assess the effect of selpercatinib on male and female fertility. A concern for female fertility is confirmed considering notably the findings observed at subclinical exposure levels in minipig studies (ovarian atrophy, decreased corpora lutea, corpora luteal cysts). In male rats, germ cell depletion and spermatid retention were seen from the low dose. Decreased testis weight, altered sperm parameters, and epididymal findings were also observed at the high dose level. These results are consistent with the non-reversible testicular degeneration reported at subclinical exposure levels in the repeat-dose toxicity studies conducted in rats and minipigs. Fertility of male rats was not affected in the male fertility study. However, this result does not mitigate the concerns for human male fertility considering the findings observed at low exposure multiples in the rat and minipigs studies.

In the dose-range finding embryo-foetal development study conducted in rats at doses of 50, 100 and 200 mg/kg/day, selpercatinib induced developmental toxicity embryolethality (early resorptions) at all dose levels. Exposure level at the low dose level were in the clinical range (animal-to-human exposure ratio of 1.5). In view of these findings, it is agreed that no additional embryo-foetal developmental toxicity study is needed since there is sufficient information to inform on the potential risks for humans.

In line with ICH S9 guidance, a pre- and postnatal toxicology study was not conducted and the potential effects on fertility were evaluated based on the information available from repeat-dose toxicity studies. In males and female rats, these findings were reported at exposure levels either lower than or in the range of those reached in patients at the maximal human recommended dose. Overall, findings from repeat-dose toxicity studies conducted in rats and minipigs suggest that selpercatinib may adversely impact on male and female fertility (see sections 4.6 and 5.3 of the SmPC).

Juvenile animal studies will be conducted, as part of the EMEA-002544-PIP01-18.

Based on data from animal reproduction studies and its mechanism of action, selpercatinib can cause foetal harm when administered to a pregnant woman. Women of childbearing potential have to use highly effective contraception during treatment and for at least one week after the last dose of selpercatinib. Men with female partners of childbearing potential should use effective contraception during treatment and for at least one week after the last dose of selpercatinib (see sections 4.6 and 5.3 of the SmPC).

Selpercatinib did not demonstrate phototoxic potential in the *in vitro* neutral red uptake assay in BALB/c 3T3 mouse fibroblasts.

No dedicated local tolerance testing was conducted. Given that the intended route of administration is the oral route, this is acceptable. The gastrointestinal tract was evaluated in all repeat-dose toxicology studies in Sprague-Dawley rats and minipigs.

Selpercatinib is unlikely to represent a risk for the environment following its prescribed usage in patients. A phase II environmental fate and effects assessments is not required according to the EMEA Guideline but regarding the PEC_{sw} value of Selpercatinib (0.0099 µg/L) which is close to the limit of 0.01 µg/L, in case of any extension in indication, this PEC_{sw} will be exceeded and complementary ad hoc phase II studies will be required. The applicant is recommended to submit a Phase II ERA by the end of 2021

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been reflected in the SmPC (sections 4.4, 4.5, 4.6 and 5.3).

The CHMP considers the following measures necessary to address the non-clinical issues:

The MAH is recommended to submit:

- the results of a 6-month carcinogenicity study in RasH2 transgenic mice

- the results of a 2-year carcinogenicity study in rats

- the results of a GLP-compliant non-clinical toxicology study in juvenile rats

- a Phase II ERA to reflect the patient population as reflected in the approved indication

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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**

Table 8. Listing of Completed Clinical Studies with Selpercatinib

Study Number	Study Title
LOXO-RET-18014	A 2-Part, Open-Label, Fixed-Sequence Study to Evaluate the Effects of Multiple Doses of Itraconazole and Rifampin on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects
LOXO-RET-18015	An Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects
LOXO-RET-18016	A Phase 1, Open-label, Two-part Study to Investigate the Absorption, Metabolism, Excretion, and Absolute Bioavailability of [14C]-LOXO-292 in Healthy Male Subjects
LOXO-RET-18017	An Open-Label, Fixed-Sequence Study to Evaluate the Effect of Multiple Doses of LOXO- 292 on the Single Dose Pharmacokinetics of Midazolam in Healthy Adult Subjects
LOXO-RET-18026	An Open-Label, Fixed-Sequence Study to Evaluate the Effect of Multiple Doses of LOXO-292 on the Single Dose Pharmacokinetics of Repaglinide in Healthy Adult Subjects
LOXO-RET-18032	A Single-Dose, Randomized, Double-Blind, Placebo- and Positive Controlled, 4 Way Crossover Study to Evaluate the Effect of LOXO-292 on the QTc Interval in Healthy Adult Subjects
LOXO-RET-18057	A Phase I, Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LOXO-292 in Healthy Adult Subjects
LOXO-RET-19075	An Open-Label, 3-Period, Fixed Sequence Study to Evaluate the Effect of an H2 Antagonist and a Proton Pump Inhibitor on the Single Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

Study Number	Study Title
LOXO-RET-18022	Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-292 Administered to Fasted Hepatically Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects
LOXO-RET-18023	A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

Table 9. Listing of Ongoing Clinical Studies with Selpercatinib

Study Number	Study Title
LOXO-RET-17001	A Phase 1/2 Study of Oral selpercatinib in Patients with Advanced Solid Tumours, Including RET Fusion-Positive Solid Tumours, Medullary Thyroid Cancer, and Other Tumours with RET Activation (LIBRETTO-001)
LOXO-RET-18036	A Study of Oral selpercatinib in Paediatric Patients With Advanced Solid or Primary Central Nervous System Tumours (LIBRETTO-121)
J2G-MC-JZJB (LIBRETTO-531)	A Multicenter, Randomized, Open-label, Phase 3 Trial Comparing selpercatinib to Physicians Choice of Cabozantinib or Vandetanib in Patients with Progressive, Advanced, Kinase Inhibitor Naïve, RET-Mutant Medullary Thyroid Cancer (LIBRETTO-531)
J2G-MC-JZJC (LIBRETTO-431)	A Multicenter, Randomized, Open-Label, Phase 3 Trial Comparing selpercatinib to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab as Initial Treatment of Advanced or Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer

2.4.2. Pharmacokinetics

The clinical pharmacology investigations of selpercatinib consisted of eight clinical studies in healthy volunteers and two clinical studies in special populations with hepatic dysfunction (LOXO-RET-18022) and renal impairment (LOXO-RET-18023).

One ongoing clinical Phase 1/2 study is performed in patients with advanced solid tumours, including ret fusion-positive solid tumours, medullary thyroid cancer, and other tumours with RET activation (LOXO-RET-17001, pivotal study) and another ongoing Phase 1/2 study is carried out in paediatric patients with advanced solid or primary central nervous system tumours (LOXO-RET-18036) (Table 9).

Full PK profiling has been performed in healthy volunteers whereas rich and sparse PK sampling were performed in patients.

Only PK data from patients were used to develop a Population PK model and Exposure-response analysis as presented in (Table 10).

Table 10. Modelling and PK/PD Studies

Study Number	Study Title
LOXO-292-DMPK-031	Population Pharmacokinetic and Pharmacodynamic Analysis for LOXO-292
LOXO-292-DMPK-050	Population PK, Tumor Size, and Exposure-Response Modeling and Simulation of LOXO-292 in Cancer Patients
LOXO-292-DMPK-052	Prediction of the Effect of CYP3A4 Inhibitors and Inducers on the Exposure of Selpercatinib (LOXO-292; LY3527723) in Healthy Volunteers

Bioanalysis

Throughout the clinical development, a unique HPLC/MS/MS bioanalytical method (TM17-410) was used to quantify selpercatinib in human plasma with K_2EDTA as anticoagulant in all clinical studies. The method was cross-validated and used to quantify selpercatinib in urine samples. The developed method allows quantification of selpercatinib over a concentration range of 1 ng/mL (LLoQ) to 1000 µg/mL in serum samples and over a range of 5.0 to 5000 ng/mL in urine samples.

Pharmacokinetic analyses

For single or multiple-dose studies, PK parameters evaluated in plasma include Cmax, Cmax/Dose, Cmin, Tmax, AUC0-t, AUC0-12, AUC0-12/Dose, AUC0-24, AUC0-24/Dose, AUC0-∞, AUC%extra, R_{AUC}, T1/2, λz, CL/F, and for multiple-dose studies, PK parameters evaluated in urine include Ae, CLr, and fe.

Standard non-compartmental (model-independent) pharmacokinetic methods were used to calculate PK parameters using Phoenix® WinNonlin version 8.1 (Certara, Princeton, NJ).

Population (Pop) PK, tumour size, survival and PK/PD analyses were performed based on interim data collected in the ongoing phase 1/2 study LOXO-RET-17001 in cancer patients. Pop PK and tumour size modeling were conducted based on the non-linear mixed effects modeling.

The Pop PK estimation was performed using the first-order conditional estimation with interaction (FOCEI) method implemented in NONMEM 7, version 7.4. NONMEM and R (version 3.4) were used for simulations to derive exposure metrics for the subsequent exposure-response analysis.

Absorption

After single or multiple dose administration of selpercatinib in both healthy subjects and patients with advanced malignancies, median T_{max} ranged between 2 hours indicating that absorption is rapid.

After a single dose of 160 mg in healthy volunteers, Cmax ranged from 1650 ng/mL to 2024 ng/mL and after multiple dose Cmax,ss ranged from 4082 ng/mL to 4574 ng/mL. In patients after a multiple dose of 160 mg BID at C1D1 and C1D8 geometric mean Cmax were 1120 ng/mL and 2980 ng/mL respectively.

Based on in vitro investigations, LOXO-292 was found to be a substrate of both P-gp and BCRP, and a weak inhibitor of P-gp.

LOXO-292 exhibit a pH dependent aqueous solubility with high solubility in very acidic (0.1 N HCL,) and low solubility at higher pH (pH 6.0,). Therefore given the information of the low fraction absorbed, LOXO-292 can be classified as a BCS class IV compound.

Absolute bioavailability

The absolute bioavailability of selpercatinib was estimated at around 73.2% (individual subject values ranging from 60.2 - 81.5%) following an oral dose of 160 mg selpercatinib capsule formulation (2x80 mg) in the fasted state and intravenous administration of approximately 9.92 µg (~ 1 µCi) of [14C]-LOXO-292.

Relative bioavailability/Bioequivalence

Two selpercatinib capsule strengths (40 mg and 80 mg) are claimed to be marketed, however only the 80 mg strength was used during the B/R pivotal study (LOXO-RET-17001) and in all the clinical pharmacology studies. Therefore, there is no clinical exposure data available for the 40 mg capsule. However the 40-mg and 80-mg capsule formulations, which differ only in their capsule shell, are expected to perform equivalently in vivo.

Influence of food

The food effect on selpercatinib PK was evaluated in 20 healthy volunteers (study LOXO-RET-18015) who were administered a single oral dose of 160 mg selpercatinib in the fasted (Period 1) and fed state (Period 2). PK results indicated that the geometric mean of selpercatinib C_{max} decreased moderately by 14% and AUC_{0-inf} increased by only 9% after administration of a high-fat breakfast (see Figure 3). The geometric mean ratio (90% CI) of Cmax and AUC_{0-inf} were 86.24 (57.27, 129.88) and 108.58 (81.17, 145.25), respectively. In the fed state, median Tmax was delayed to approximately 4 hours postdose.

The effect of administration of PPI (omeprazole) on selpercatinib PK was also investigated in 20 healthy volunteers who were administered multiple QD dose of omeprazole and a single oral dose of 160 mg selpercatinib in the fasted (Period 3) and fed state (Period 4). PK results indicated in the fasted state that the geometric mean of selpercatinib C_{max} decreased highly by 88% and $AUC_{0\text{-}inf}$ decreased by 69% whereas in the fed state, there were no significant change in PK parameters exposure except for Cmax which decreased by 50%. In the fasted state, median Tmax was delayed to approximately 2.5 hours postdose whereas in the fed state Tmax was delayed at 6h postdose.

These data support that selpercatinib capsules could be administered with or without regards to food.

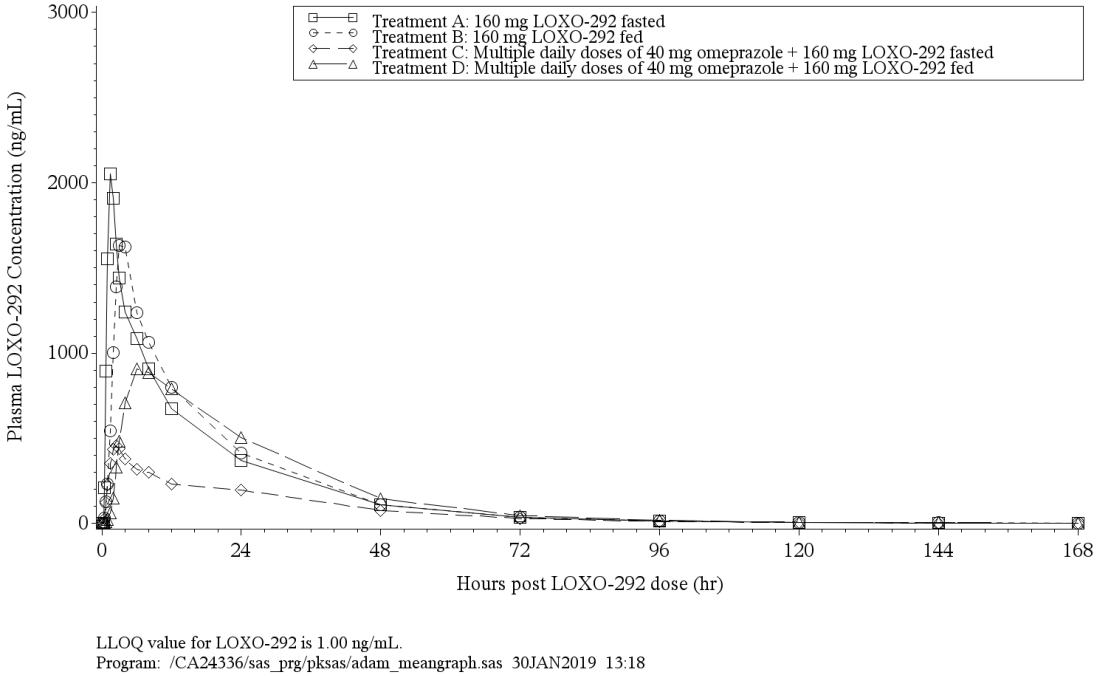


Figure 3. Mean plasma LOXO-292 concentration time profiles following administration of 160 mg LOXO 292 fasted (treatment A), fed (Treatment B), co-administration of multiple dose omeprazole +160 mg LOXO-292 fasted (Treatment C), and co-administration of multiple dose omeprazole +160 mg LOXO-292 fed (Treatment D)

Distribution

Based on in vitro investigations (LOXO-292-DMPK-012), selpercatinib was found to be highly bound (96.1%) to human plasma proteins, mainly on albumin and to a lesser extent to α1− acid glycoprotein. Protein binding was independent of selpercatinib concentration from 0.1 to 20 µM.

From study LOXO-RET-18022 (hepatic impairment), the unbound fraction was confirmed at 3.89%.

In the human AME study (LOXO-RET-18016), the blood-to-plasma radioactivity ratios of AUC0-24 was determined to be 0.59, respectively, suggesting lack of meaningful distribution of selpercatinib into blood cells. Based on in vitro investigation (LOXO-DMPK-013), B/P ratio was estimated at 0.70.

Following IV dosing, in healthy volunteers the selpercatinib volume of distribution during the terminal phase (Vz) or at steady state in plasma was 127 L and 85 L respectively, whereas following oral dosing the apparent distribution volume was 307 L.

Following oral dosing of selpercatinib in patients, based on a PopPK analysis, the selpercatinib mean (CV%) estimated volume of distribution (Vss/F) was 191 L (69%).

Elimination

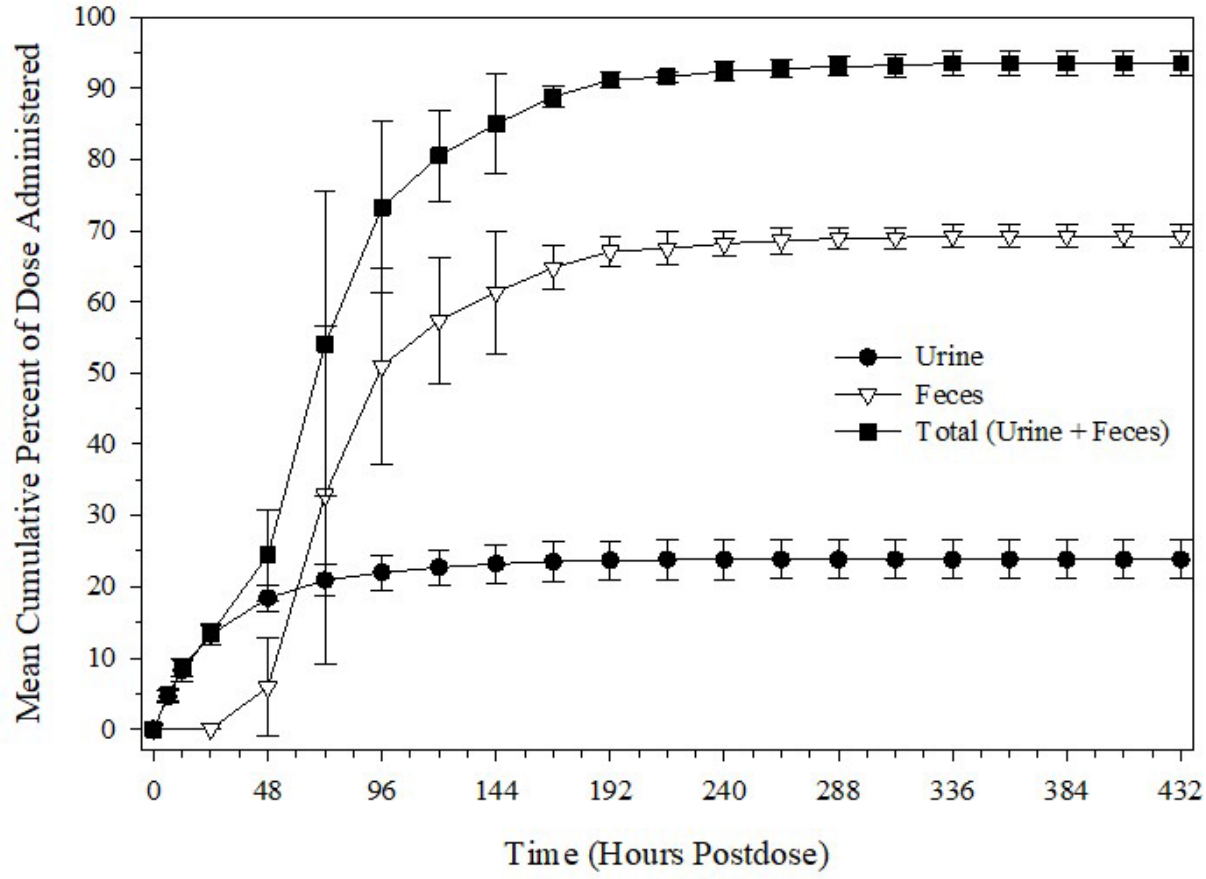
The mass balance study LOXO-RET-18016 was a two part study including both oral and IV administration of [14C]-LOXO-292 with a radiolabelled dose (160 mg ~40 µCi) and a microtracer design of the IV dose (~ 9.92 µg ~1µCi) administered to 6 healthy volunteers. Results are provided in Table 11.

Table 11. Summary of Absorption, Metabolism and Excretion Parameters of LOXO-292 in Study LOXO-RET-18016.

Parameter	Part 1 160 mg, (40 µCi)[a] Oral Solution Dose	Part 2 160 mg (nonlabeled) Oral Capsule Dose	Part 2 ~10 µg, (1 µCi)[b] IV Dose
Selpercatinib Plasma PK Parameters, Geometric Mean (Geometric %CV)			
AUC_{last} (h*ng/mL)	24100 (20.2)	20200 (26.6)	1.68 (30.0)
$AUC_{0-\infty}$ (h*ng/mL)	NA	20300 (26.6)	1.72 (33.5)c
C_{max} (ng/mL)	1890 (22.7)	1550 (28.0)	0.201 (30.0)
T_{max} (h), median (range)	1.25 (1.00, 1.50)	1.92 (1.00, 1.92)	0.167 (0.167, 2.10)
$t_{1/2}$ (h), arithmetic mean (SD)	36.5 (18.0)	31.5 (20.7)	16.9 (7.97)c
CL/F (L/h)	6.83 (20.2)	7.89 (26.6)	NA
CL (L/h)	NA	NA	5.70 (33.4)c
V_z/F (L)	NA	NA	NA
V_z (L)	NA	NA	127 (56.8)c
Absolute Oral Bioavailability	NA	0.732 (13.9)c	NA
Selpercatinib and Metabolites in Plasma (Fraction of Radioactivity in a Pooled Plasma Sample Representing $AUC_{1\text{-}168\ hours}$)			
Selpercatinib (%)	86.17	-	-
Metabolites M2, M3, M4, M5 (%)	< 4% each	-	-
Renal Excretion (Selpercatinib)			
Fe (%)	11.5	7.34 (27.9)	13.5 (24.2)
Clr (L/h)	-	0.579 (29.4)	0.789 (37.6)c
Excretion Mass Balance (Selpercatinib + Metabolites), Mean (%CV)			
Urine (%)	23.8 (2.72)	NA	30.2 (4.3)
Feces (%)	69.3 (1.60)[c]	NA	60.3 (10.7)
Total (%)	93.5 (1.75)[c]	NA	90.7 (5.8)

Following oral dosing, the overall recovery of radioactivity in this mass balance study was high (93.5% ± 1.75%), with 69.3% ± 1.60% of the dose recovered in feces and 23.8% ±2.72% recovered in urine (Figure 4). Approximately 14% and 11.5% of [14C]-LOXO-292 was recovered unchanged in feces and urine respectively. Renal clearance was found to be low and estimated at 0.579 L/h. this low renal clearance was also confirmed in patients, estimated at 0.432 L/h (160 mg BID dose, Study LOXO-RET-17001). Excretion was relatively rapid with most of the administered radioactivity (85%) excreted in 144 hours.

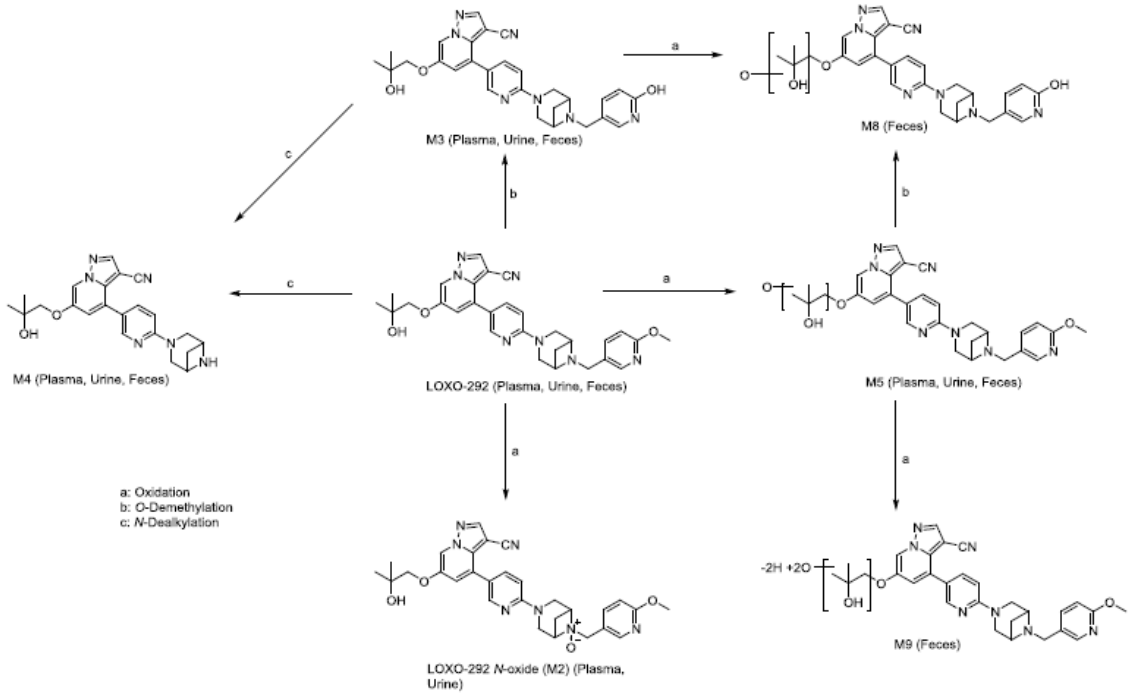
Figure 4. Arithmetic mean (±SD) cumulative percent of radioactive dose recovered in urine (N=6 subjects) and faeces (n=5 subjects) after a single oral dose of [14C]-LOXO-292 160 mg (~40 µCi) to healthy male



Following IV dosing, the overall recovery of radioactivity in this mass balance study was high (90.7% ± 5.8%), with 60.3% ± 10.7% of the dose recovered in feces and 30.2% ±4.3% recovered in urine. Approximately 13.5% of [14C]-LOXO-292 was recovered unchanged in urine. Similarly renal clearance was found to be low, estimated at 0.789 L/h.

LOXO-292 underwent extensive metabolism (Figure 3) which involved the formation of 6 oxidized metabolites. *O*-Demethylation was the main biotransformative pathway to produce desmethyl-LOXO-292 (M3), followed by *N*-dealkylation to produce *N*-dealkylated-LOXO-292 (M4). Two other oxidative metabolites, oxy-LOXO-292 (M5), which was oxidized on the aliphatic portion of LOXO-292, and LOXO-292 *N*-Oxide (M2), were present in minor to trace amounts. Metabolites M5 and M3 underwent further oxidation to produce metabolites carboxy-LOXO-292 (M9) and oxy-desmethyl-LOXO-292 (M8), respectively, and were only present in feces in minor amounts. In plasma the parent compound accounted for 86.17 of the total radioactivity with no major metabolite (≥ 10% of total compound-related material) were detected. In both urine and faeces more than 98% of the recovered radioactivity was identified. None of the metabolites (M2, M3 and M4) have an activity on RET kinase more potent than selpercatinib.

Figure 5. Proposed biotransformation pathways of LOXO-292 after a single oral dose of [14C]-LOXO-292 160 mg (~40 µCi) to healthy male



Based on in vitro investigations using human recombinant CYP enzymes, selpercatinib was found to be predominantly metabolized by CYP3A4. In addition, selpercatinib showed weak inhibition of CYP2C8, with an IC50 values of 3.4 µM, and weak time-dependent inhibition of CYP3A4 with KI of 9 µM, kinact of 0.013 min^{-1} (kinact/KI of 0.0014 min^{-1} μM^{-1}, this turn to R = 1.4, LOXO-292-DMPK-010).

Across healthy subjects, studies (including DDI studies presented later in the DDI part) following single oral dose of 160 mg the geometric mean terminal half-life for selpercatinib was in the range of 20.6 to 31.2 hours. The mean apparent clearances (CL/F) for selpercatinib in healthy volunteers were estimated between 6.58 to 7.89 L/h. In patients after MD of 160 mg BID, CL/F was estimated at 6.2 L/h with a calculated half-life of 22 hours, based on the results from the PopPK analysis.

Dose proportionality and time dependencies

Dose proportionality

Based on PK data from patients following BID dosing of ascending doses of selpercatinib (Study LOXO-RET-17001), selpercatinib exposures PK parameters increase with increasing dose at C1D1 and at C1D8 (Table 12 and Figure 6).

LOXO-292 exhibits linear to supra-proportional PK in patients from 20 mg QD to 240 mg BID.

Table 12. Summary of Plasma LOXO-292 PK Parameters by Actual Dose of Capsule Formulation (C1D8)

		CYCLE 1 DAY 8								
ACTUAL DOSE		T_{max}[a] (h)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (h*ng/mL)	AUC_{tau} (h*ng/mL)	$AUC_{0\text{-}24}$ (h*ng/mL)	R_{AUC}	CL_{ss}/F (L/h)	C_{max}/Dose (ng/mL/mg)	AUC_{tau}/Dose (h*ng/mL/mg)
20 mg QD	N	6	6	6	6	6	5	6	6	6
	GM	1.05	123	1330	1330	1330	1.97	15.1	6.13	66.4
	GCV%	0.00, 2.25	220.6	137.1	137.1	137.1	18.1	137.1	220.6	137.1
20 mg BID	N	9	9	9	9	9	9	9	9	9
	GM	1.88	275	2290	2290	4580	2.66	8.73	13.7	115
	GCV%	0.00, 2.25	53.2	49.8	49.8	49.8	58.1	49.8	53.2	49.8
40 mg BID	N	16	16	16	16	16	16	16	16	16
	GM	2.03	546	4600	4600	9200	2.90	8.70	13.6	115
	GCV%	0.967, 6.08	50.7	48.3	48.3	48.3	88.4	48.3	50.7	48.3
60 mg BID	N	12	12	12	12	12	11	12	12	12
	GM	2.02	1070	8870	8870	17700	2.47	6.76	17.9	148
	GCV%	1.12, 4.08	45.0	45.6	45.6	45.6	50.5	45.6	45.0	45.6
80 mg BID	N	20	20	20	20	20	19	20	20	20
	GM	2.01	1340	10800	10800	21600	2.63	7.39	16.8	135
	GCV%	0.00, 4.02	49.0	55.0	55.0	55.0	52.8	55.0	49.0	55.0
120 mg BID	N	17	17	17	17	17	13	17	17	17
	GM	2.00	2300	19100	19100	38300	3.19	6.27	19.2	159
	GCV%	0.00, 4.00	47.4	53.3	53.3	53.3	53.7	53.3	47.4	53.3
160 mg BID	N	410	410	410	402	402	92	402	410	402
	GM	2.00	2980	25600	25800	51600	3.43	6.20	18.6	161
	GCV%	0.00, 8.10	53.1	57.7	57.9	57.9	68.3	57.9	53.1	57.9
200 mg BID	N	3	3	3	3	3	3	3	3	3
	GM	2.13	2650	22000	22000	43900	3.21	9.10	13.3	110
	GCV%	1.10, 4.00	45.6	30.3	30.3	30.3	127.9	30.3	45.6	30.3
240 mg BID	N	5	5	5	5	5	5	5	5	5
	GM	2.12	5270	43900	43900	87900	2.88	5.46	22.0	183
	GCV%	1.87, 4.08	18.4	23.1	23.1	23.1	97.1	23.1	18.4	23.1

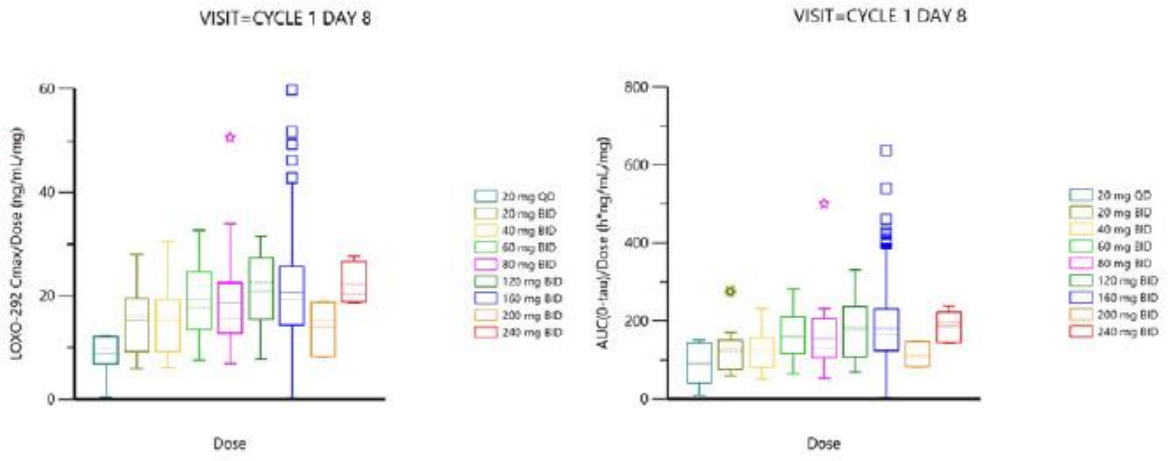


Figure 6. Dose-normalized plasma LOXO-292 Cmax and AUC0-t at steady-state

Time dependency

Based on study LOXO-RET-18016 (mass-balance Part 2, Table 11), with a mean estimated half-life of 31.5 h, in healthy volunteers, steady state is expected to be reached after a week following a multiple dose of 160 mg BID of LOXO-292. This is confirmed by both studies LOXO-RET-18017 and LOXO-RET-18026 performed in healthy volunteers.

Following 160 mg BID dosing of selpercatinib in patients (Study LOXO-RET-17001), PK sampling at Day 8 were considered at steady-state. Estimated half-life was 22h, Geometric mean Racc was estimated at 3.43 and $AUC_{0\text{-}24h}$ was 51,600 (58%) ng*h/mL (Table 12).

Special populations

Intra- and inter-individual variability

Across studies and using NCA approach, the between-patient variability in selpercatinib was moderate to high ranging from 38% to 85.6 % for Cmax, and ranging from 24.4 to 78.5 % for AUCs (variability shown as CV %).

Data from Pop PK analysis showed very high between-patient variability for absorption related parameters ka and Dur (CV= 78 and 56%, respectively) and for Vc/F (CV = 69%). A bit lower IIV was estimated for CL/F = 49% but remains relatively high. The magnitude of the proportional errors was moderate (CV = 28%).

PK Population analyses

Additional to formal PK investigations in healthy volunteers, the applicant has performed Pop PK analyses in order to describe and identify sources of variability of selpercatinib after repeated administration in cancer patients.

LOXO-RET-17001

The study is ongoing. Briefly, patients with advanced solid tumours, including RET fusion-positive solid tumours, RET-mutant MTC, and other tumours with RET activation, received oral ascending doses of selpercatinib ranging from 20 mg once daily (QD) through 240 mg twice daily (BID) during phase 1. The dose of 160 mg BID was selected for Phase 2.

LOXO-292-DMPK-050

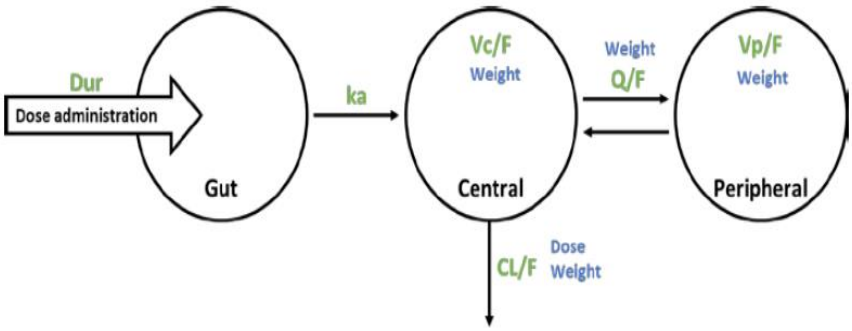
The final dataset included a total of 6379 PK observations from 512 patients, with 6246 non-BLQ and 133 BLQ PK observations (2.1% <5%). The median number of PK observations per patient was 5, and the range was 1 to 68 observations. All BLQ PK observations were excluded from the analysis.

The majority of patients included in the analysis received the dose 160 mg BID (n= 465, 91%) followed by 80 mg BID (n= 57, 11%), 120 mg BID (n=34, 6,6%) and 60 mg BID (n=33, 3,5%). To note, due to dose adjustments, some patients received multiple dose levels of selpercatinib during the study and are counted more than once.

The final Pop PK model retained for selpercatinib after oral administration is a 2-compartment disposition model with sequential zero (DUR) and first-order absorption (ka), with a linear elimination and a combined multiplicative and additive errors model. Inter-individual variability (IIV) terms are included on CL/F, Vc/F, ka, and Dur with a correlation between the IIV terms for CL/F and Vc/F.

A diagram of the final population PK model is presented in Figure 7. Parameter estimates for the final population PK model are presented in Table 13.

Figure 7. Diagram of final population PK model for LOXO-292



Abbreviations: CL/F=apparent clearance; Dur=duration of zero-order absorption; ka=first-order first-order absorption rate constant; PK=pharmacokinetic; Q/F=apparent intercompartmental clearance; Vc/F=apparent central volume of distribution; Vp/F=apparent peripheral volume of distribution.

Table 13. Parameters of the Final Population PK Model

	Estimate		Interindividual Variability		
Parameter (unit)	**Typical Value**	**RSE[a]**	**Typical Value**	**RSE[a]**	**Shrinkage[b]**
Apparent clearance (CL/F, L/hr)	6.0	2.4%	49%	4.1%	2.9%
Effect of Dose on CL/F (%/mg)[c]	-0.3%	24%	—	—	—
Apparent distributional clearance (Q/F, L/hr)	27	8.0%	—	—	—
Apparent central volume of distribution (Vc/F, L)	101	5.8%	69%	7.2%	27%
Apparent peripheral volume of distribution (Vp/F, L)	90	4.5%	—	—	—
First-order absorption rate constant (ka, 1/hr)	1.51	6.7%	78%	13%	50%
Zero-order absorption duration (Dur, hr)	1.04	3.1%	56%	5.6%	50%
Correlation between IIV-CL/F and IIV-Vc/F	—	—	34%	10%	—
Residual variability					
Proportional residual error	28%	4.3%	—	—	7.1%
Additive residual error SD (ng/mL)	47	16%	—	—	7.1%

The magnitude of the proportional errors was moderate (28%) and the additive error was estimated at 47 ng/L (acceptable when compared to geometric mean steady state C_{max} = 2980 ng/L). A large IIV was observed for absorption related parameters (CV= 78 and 56% for Ka and Dur, respectively) and for Vc/F (CV = 69%). A bit lower IIV was estimated for CL/F = 49% but remains relatively high.

Two covariates (dose and body weight) were identified as significant parameters of PK variability.

a) Non-linearity was identified on CL/F, which decreased with increasing dose. This leads to greater-than-proportional increases in selpercatinib exposure with increasing dose levels. CL/F decreases significantly (by around one half) from 8.3 to 4,6 L/hr when dose levels of selpercatinib increases from 20 to 240 mg. At the proposed clinical dose level of 160 mg BID, the typical value reported for CL/F is 5.9 L/hr.

b) BW was included in the final Pop PK model following allometric principles where volume parameters increase proportionally to body weight (exponent is 1) and clearance parameters increase slightly less than proportionally to body weight (exponent is 0.75). For illustration, CL/F increases by more than 50% for a BW of 107.08 kg by comparison to the typical value observed with a reference BW of 70 Kg. In contrast, CL/F decreases by more than 30% for a BW of 45.9 kg compared to the typical CL/F value observed with a reference BW of 70 kg. The same impact was also observed for Vd/F and Vp/F but in a lesser degree; the relative change was +40% for a BW of 107.08 kg and -25% for a BW of 45.9 kg compared to typical volumes values.

In general, the population typical values and covariate effects were precisely estimated (low RSE% <10%, except for the dose covariate on CL/F where RSE was 24%). Bootstrap results were based on 954 (95%) runs out of 1000 replicates and are in good concordance with the final parameter estimates. Low eta shrinkage was associated with CL/F (2,3%), whereas medium to high eta shrinkage was observed for Vc/F and the absorption parameters Ka and DUR (27%, 50% and 50%, respectively). Prediction-corrected VPC for all data (Figure 8) suggest that the model describes well the observed

data, despite some overprediction at times <1 hour postdose, with little impact on predicting steady-state Cmax and Cmin).

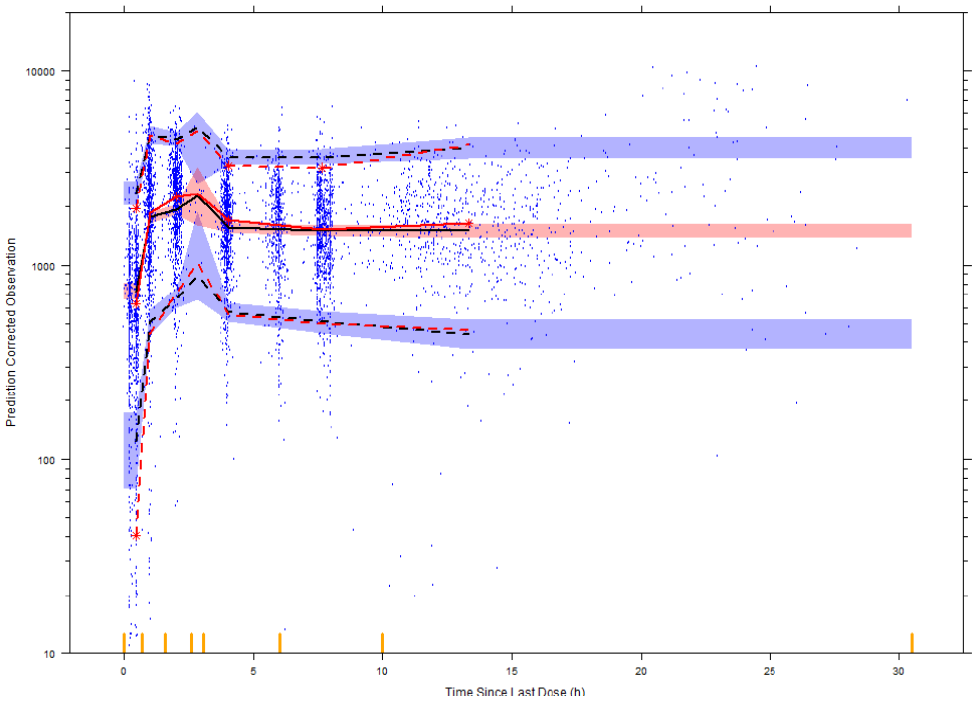


Figure 8. Prediction-corrected VPC of the final population PK Model for selpercatinib

Impaired hepatic function

A formal dedicated study (LOXO-RET-18022) investigating the effect of various degree of hepatic impairment on PKs of selpercatinib was performed. Selpercatinib AUC0-∞ increased by 7% in subjects with mild, 32% in subjects with moderate Child Pugh classification. Thus, selpercatinib exposure (AUC) in subjects with mild and moderate hepatic impairment (Child Pugh class A and B) is comparable to exposure in healthy subjects when a dose of 160 mg is administered. Selpercatinib AUC0-∞ increased by 77% in subjects with severe hepatic impairment (Child Pugh class C).

Impaired renal function

The effect of renal impairment on the pharmacokinetics of selpercatinib was evaluated in a renal impairment study in subjects with normal renal function, mild, moderate (⩾30 and <60 mL/min/1.73 m2) and severe (<30 mL/min/1.73 m2) renal impairment (LOXO-RET-18023). In subjects with mild and moderate renal impairment, the geometric mean Cmax and AUC0-∞ were similar to that of normal subjects. For severe renal impairment whereas a prolonged half-life is observed compared to other groups and normal subject 33.8h vs 24.8 h, PK parameter exposures (Cmax and AUC0-∞) appear similar between severe vs normal renal patients.

End stage renal disease (eGFR <15 ml/min) and dialysis patients have not been studied.

Age, sex, Race

No formal investigations in matched groups with regard to intrinsic factors (age, sex and race) have been performed. Age, sex and race have been tested as covariates in the population PK modeling and no clinically relevant effect on the PKs of selpercatinib was observed.

Weight

The effect of weight on the PKs of selpercatinib was investigated in patients based on a Pop PK approach.

Based on the population PK analysis, BW was found to be a significant covariate on Vc/F, Vp/F, CL/F and Q/F parameters and therefore was retained in the final Pop PK model. BW was included following allometric principles, where volume parameters (Vc/F, Vp/F) increase proportionally to BW (exponent is 1.0) and clearance parameters (CL/F and Q/F) increase slightly less than proportionally to BW (exponent is 0.75). Indeed, CL/F was found to increase by more than 50% for a BW of 107.08 kg by comparison to the typical value of CL/F for patient weighting 70 Kg. In contrast, CL/F decreased by more than 30% for a BW of 45.9 kg compared to the typical CL/F value for a BW of 70 kg. The same impact was also observed for Vd/F and Vp/F but in a lesser degree; the relative change was +40% for a BW of 107.08 kg and -25% for a BW of 45.9 kg compared to typical volumes values for a reference BW of 70 Kg.

Further investigation of the impact of BW on the systemic exposure of selpercatinib at steady state indicated clearly that a clinically relevant change (>30%) is observed on $AUC_{0\text{-}24h}$, C_{min} C_{max} in patients with extreme BW (<45.9 and >107.1 kg) compared to a typical patient with median weight of 68 kg. Additional data show a significant change of the median AUC and Cmax between patient's ≤ 50 kg and > 50 kg, confirming the influence of BW on exposures endpoints and consequently the need for a dose adjustment based on BW.

Elderly

The effect of age on the PKs of selpercatinib was investigated in patients based on a Pop PK approach.

- The mean (±SD) age was 57,6 years (±13,5). The median (min; max) BW was 59 kg (15; 90). However, among the 512 patients included in the dataset, the number of elderly subjects included in the different subgroups of age: [65 to 74 years], [75 to 84 years] and >85 years old is not known.

Age (tested as a continuous covariate) was not identified as a relevant covariate influencing PK parameters (CL/F, Vc/F, Ka, Dur) of selpercatinib. Therefore, no dose adjustment is required based on age.

Table 14. Clinical pharmacology studies in elderly (> 65 or more)

	Age 65-74 years (number of older subjects /total number)	Age 75-84 years (number of older subjects /total number)	Age 85+ years (number of older subjects /total number)
PK Trials	9	0	0 (in std clinical pharmaceutical studies)
LOXO-RET-17001 popPK	133/512	39/512	3/512

Paediatrics

A study of selpercatinib in paediatric patients (LOXO-RET-18036) is ongoing. However, no PK data are yet available from this study. Based on the known clearance pathway of selpercatinib (CYP3A4) and CYP3A4 maturation by the age of 6 months, the dose of 92 mg/m2 BID with a maximum dose of 160 mg BID was considered appropriate for paediatric patients to result in paediatric exposure (AUC) similar to that of adult patients in study LOXO-RET-17001.

Healthy volunteers

In all Phase 1 studies a 160 mg QD or BID dose or dose up to 720 mg QD with only 1 formulation (30% blend capsule of 80 mg) have been investigated. In patients, dose from 20 mg QD and 20 mg

BID to 240 mg BID was investigated with all developed formulations (20 mg capsule unmilled, 10 mg/20 mg/80 mg 30% blend capsule and liquid formulation).

The PopPK analysis was developed only with PK data from patients. No comparison of the PK parameters between HV and patients have been performed by the applicant.

Pharmacokinetic interaction studies

In silico

Multiple PBPK models using Symcip platform were developed including models for selpercatinib, the CYP3A4 inducers, bosentan, modafinil, and rifampin, and the CYP3A4 inhibitors itraconazole, clarithromycin, diltiazem, and fluconazole. They were verified and sensitivity analysis were performed. This allowed determination of effects of CYP3A4 inducers and inhibitors: for example, CYP3A4 moderate inducers caused a decrease in the single dose AUC of selpercatinib of 36-47%. CYP3A4 inhibitors caused an increase in the single dose AUC of selpercatinib of 2.2- to 3.8-fold.

In vivo

The PK of selpercatinib appeared to be sensitive to gastric pH under fasted conditions based on the concomitant use of the proton pump inhibitor omeprazole, with a decreased exposure at higher pH. PK results indicated in the fasted state that the geometric mean of selpercatinib C_{max} decreased highly by 88% and $AUC_{0\text{-}inf}$ decreased by 69% whereas in the fed state, there were no significant change in PK parameters exposure except for Cmax which decreased by 50%. Administration of the H2 antagonist ranitidine given under fasted conditions had no effect on selpercatinib overall exposure.

Based on in vitro investigations, selpercatinib was found to be predominantly metabolized by CYP3A4. An effect of CYP3A4 inhibitor and inducer was shown.

Therefore, the clinical drug interaction trial (LOXO-RET-18014) was conducted with the strong CYP3A4 inhibitor (multiple-dose itraconazole) and a strong CYP3A4 inducer (multiple-dose rifampin).

Multiple-dose steady-state administration of itraconazole resulted in an increase of approximately 130% and 30% in selpercatinib AUC and Cmax, respectively, compared to selpercatinib alone.

Multiple-dose steady-state administration of a strong CYP3A4 inducer (rifampin) resulted in a decrease of approximately 87% and 70% in selpercatinib AUC and Cmax, respectively, compared to selpercatinib alone.

In addition, selpercatinib showed weak inhibition of CYP2C8 in *in vitro* investigations. These findings were therefore studied in two clinical DDI studies LOXO-RET-18017 with midazolam as probe, and LOXO-RET-18026 with repaglinide as probe.

Study LOXO-RET-18017 investigated effect of multiple dose selpercatinib on the single-dose PK of midazolam, a sensitive CYP3A4 substrate.

Multiple-dose steady-state administration of 160 mg BID selpercatinib resulted in an increase of approximately 54% and 39% in midazolam AUC and Cmax, respectively, compared to midazolam alone

Multiple-dose steady-state administration of 160 mg BID selpercatinib resulted in an increase of approximately 27% and 6% in 1-hydroxymidazolam AUC and Cmax, respectively, compared to midazolam alone

The increase in exposures to midazolam and 1-hydroxymidazolam were within the range of ≥ 1.25- to < 2-fold; indicating that selpercatinib is a weak inhibitor of CYP3A4.

Interactions with repaglinide, a sensitive CYP2C8 substrate, was investigated in study LOXO-RET-18026. Selpercatinib increased the Cmax and AUC of repaglinide (a substrate of CYP2C8) by approximately 188% and 91% respectively.

The increases in overall exposure (based on AUCs) to repaglinide were within the range of = 2 to < 5-fold, indicating that selpercatinib is a moderate inhibitor of CYP2C8.

To determine the magnitude of the effect of a P-gp inhibitor on Selpercatinib PK, a clinical drug interaction trial with a P-gp inhibitor (LOXO-RET-18014), single-dose rifampin, was conducted. Selpercatinib exposure was increased minimally by co-administration of rifampicin (increase of approximately 6.5% and 19% in selpercatinib AUC0-24 and Cmax, respectively).

MATE1 contributes to the renal excretion of creatinine and its inhibition can cause changes in serum creatinine. The in vivo inhibition of MATE1 was evaluated by review of the change in serum creatinine caused by administration of 160 mg BID Selpercatinib for 10 days to healthy volunteers (LOXO-RET-18017 and LOXO-RET-18026). Serum creatine increased slightly in all subjects.

2.4.3. Pharmacodynamics

Mechanism of action

The mechanism of action of selpercatinib is based on the evidence of non-clinical studies, pharmacokinetics and PK/PD modelling, no human mechanistic data have been provided.

Primary and Secondary pharmacology

Related to primary pharmacology, only PK/PD models were provided with the PD data from LIBRETTO-001 study.

In relation to secondary pharmacology, a single-dose, randomized, double-blind, placebo- and positive controlled, 4 way crossover study to evaluate the effect of selpercatinib on the QTc interval in healthy adult subjects was submitted (LOXO-RET-18032). In 32 healthy subjects, no large change (that is, >20 ms) in the QTcF interval was detected at selpercatinib concentrations similar to those observed with a therapeutic dosing schedule.

PK/PD modeling

A tumour size model was presented as an exploratory model.

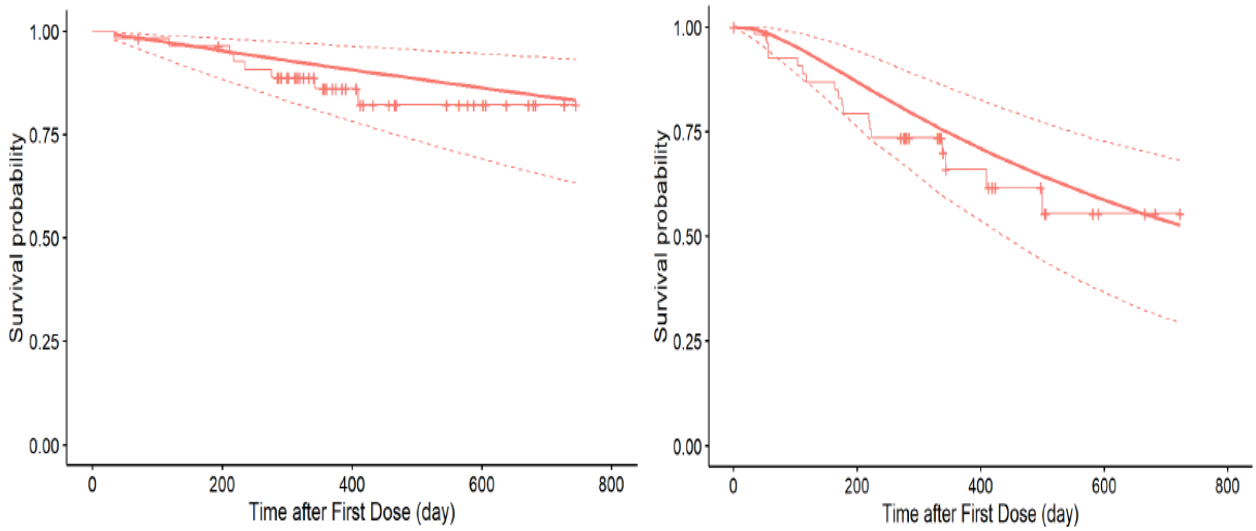
Exposure-response relationships

Survival analyses (ER-efficacy)

- A survival model was built to describe the observed efficacy endpoints [Overall Survival (OS) and progression-free survival (PFS)], with tumour size changes as a predictor. Instead of the Pop PK, tumour size and safety exposure-response analyses, this analysis included only data from patients in the primary analysis of the ongoing phase 1/2 Study LOXO-RET-17001: n=105 patients with RET fusion-positive NSCLC and n=55 patients with RET-mutant. Survival data up to 700 days were available.

- The analysis was performed separately for the two tumour groups (n= 105 patients with RET Fusion NSCLC and n= 55 patients with RET Mutant MTC). Possible predictors including age, race, sex, prior therapy radiation, prior surgical therapy and tumour shrinkage ≥30% were investigated. Based on the

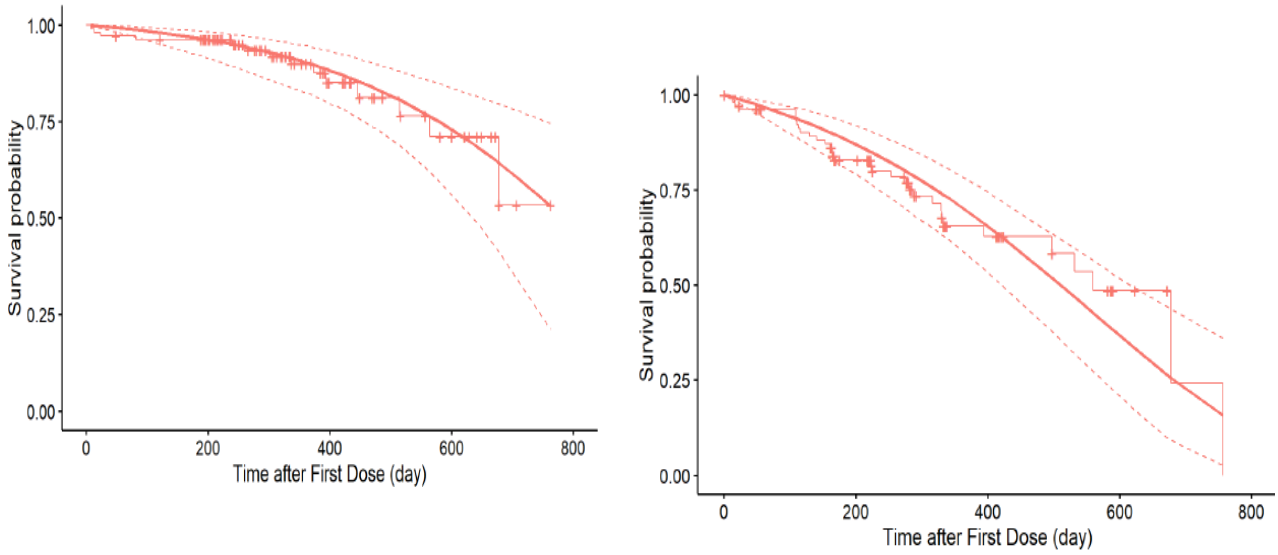
univariate Kaplan-Meier survival curves, tumour shrinkage was found to be a significant (p-value p<0.01) predictor for both OS and PFS for both tumour groups using a parametric survival model. A Gompertz model was retained for both OS and PFS RET fusion NSCLC and exponential and log-normal distributions were selected for OS and PFS RET Mutant MTC, respectively.



Abbreviations: CI=confidence interval; OS=overall survival.

The thin line represents observed survival, thick line represents the parametric survival model fit, dashed lines represent the 90% CI for the parametric survival model fit, and plus signs represent last time point for censored individuals.

Figure 9. Parametric survival curves and model fit for OS (left) and PFS (right) for RET mutant MTC



Abbreviations: CI=confidence interval; OS=overall survival.

The thin line represents observed survival, thick line represents the parametric survival model fit, dashed lines represent the 90% CI for the parametric survival model fit, and plus signs represent last time point for censored individuals.

Figure 10. Parametric Survival Curves and Model Fit for OS (left) and PFS (right) for RET Fusion NSCLC

Safety exposure-response

- As for the Pop PK analysis, the safety exposure-response analyses used the same interim data from the ongoing phase 1/2 study LOXO-RET-17001. The dataset included n= 512 patients (cut-off date of 17 June 2019). The analyses examined 4 different adverse events (AEs):

- Increases in alanine aminotransferase (ALT),

- Increases in aspartate aminotransferase (AST),

- Hypersensitivity and,

- hypertension.

Among 512 patients, it is noteworthy that only 45 (9%), 34 (7%), 5 (1%) and 71 (14%) patients developed an increase of ALT, increase of AST, hypersensitivity, and hypertension, respectively.

- Based on the provided results, none of the predictors (dose, AUC_{ss24h}, C_{min}, age, race, body weight, sex, and tumour group) were statistically significant for the prediction of increase in ALT, increase in AST or hypersensitivity AEs. Age was the only predictor of the incidence of hypertension. The reference patient in this analysis is 59 years old and has a 13.8% probability of experiencing a hypertension AE. A patient 38 years of age (10th quartile of observed data) has an odds ratio (OR) of 0.6 relative to the reference patient, and a patient 74 years of age (90th quartile of observed data) has an OR of 1.45 relative to the reference patient.

2.4.4. Discussion on clinical pharmacology

The single HPLC/MS/MS bioanalytical method (TM17-410) used to quantify selpercatinib in human plasma (K_2EDTA as anticoagulant) in all clinical studies appears to be adequate and comply with acceptance criteria of the bioanalytical method validation EMA Guideline (EMEA/CHMP/EWP/192217/2009 Rev. 1).

Additionally to investigation in formal PK studies, Pop PK, tumour size, survival and PK/PD analyses were performed based on interim data collected in the ongoing phase 1/2 study LOXO-RET-17001. These analyses utilized a dataset available up to the data cut-off date of 17 June 2019.

During phase I of study LOXO-RET-17001, patients received repeated ascending doses ranging from 20 mg QD to 240 mg BID. In phase 2 part, the dose of 160 mg BID was selected. Therefore, the majority of patients included in the modelling analyses received 160 mg BID dose (n= 465, 91%) followed by 80 mg BID (n= 57, 11%), 120 mg BID (n=34, 6,6%) and 60 mg BID (n=33, 3,5%).

Overall, the final Pop PK model for selpercatinib could be considered adequate to describe observed data.

Body weight affects selpercatinib exposure metrics as higher systemic exposure (AUC0-24h and Cmax) was observed in patients with lower body weights. Based on exposure-matching and avoidance of excess of adverse events (especially with regards to the concentration dependant QTC prolongation risk), and taking into account the relevant range of body weight for both adults and adolescents (≥ 12 years), it is recommended that patients with a body weight ≤50 kg should start selpercatinib treatment with a dose of 120 mg twice daily, while patients >50 kg should start selpercatinib treatment with a dose of 160 mg twice daily.

In a thorough QT study, no large change (that is, >20 ms) in the QTcF interval was detected at selpercatinib concentrations similar to those observed with a therapeutic dosing schedule. An exposure-response analysis (data not shown) indicated that supra therapeutic concentrations, could lead to an increase in QTc > 20 ms (see sections 4.2, 4.4, 5.1 of the SmPC).

Safety exposure-response analyses do not establish clear relationships between the systemic exposures of selpercatinib (doses up to 160 mg BID) and the likelihood of occurrence of the investigated AEs: increase in ALT, AST, hypersensitivity or hypertension.

Age (range: 15 years to 90 years) or gender had no clinically meaningful effect on the pharmacokinetics of Retsevmo. No dose adjustment is required based on age (see sections 4.2 and 5.2 of the SmPC).

Close monitoring of patients with impaired hepatic function is important. Based on submitted data, no dose adjustment is required for patients with Child Pugh mild or moderate hepatic impairment. Patients with Child Pugh severe hepatic impairment should be dosed with 80 mg selpercatinib twice daily (see sections 4.2 and 5.2 of the SmPC).

In a clinical pharmacology study using single dose selpercatinib 160 mg, exposure (AUC) was unchanged in subjects with mild, moderate, or severe renal impairment, therefore dose adjustment is not necessary in these patients. End stage renal disease (eGFR <15 ml/min) and dialysis patients have not been studied.

Based on limited pharmacokinetic data, the Cmax and AUC was similar in adolescent patients, 12-18 years of age, and in adults.

Sepercatinib metabolism is through CYP3A4. Therefore, medicinal products that can influence CYP3A4 enzyme activity may alter the pharmacokinetics of selpercatinib. If strong CYP3A and/or P-gp inhibitors, including, but not limited to, ketoconazole, itraconazole, voriconazole, ritonavir, saquinavir, telithromycin, posaconazole and nefazodone, have to be coadministered, the dose of selpercatinib should be reduced.

The concomitant use of strong CYP3A4 inducers including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (Hypericum perforatum), should be avoided (see sections 4.2, 4.4 and 4.5 of the SmPC).

Selpercatinib showed inhibition of CYP2C8 and CYP3A4, therefore coadministration with sensitive CYP2C8 substrates (e.g., odiaquine, cerivastatin, enzalutamide, paclitaxel, repaglinide, torasemide, sorafenib, rosiglitazone, buprenorphine, selexipag, dasabuvir and monteukast), should be avoided.

Similarly, concomitant use with sensitive CYP3A4 substrates, (e.g., alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, tipranavir, triazolam, vardenafil), should be avoided.

Co-administration with multiple daily doses of omeprazole (a proton pump inhibitor) decreased selpercatinib AUC0-INF and Cmax when selpercatinib was administered fasting. Co-administration with multiple daily doses of omeprazole did not significantly change the selpercatinib AUC0-INF and Cmax when Retsevmo was administered with food. Selpercatinib must therefore be accompanied by a meal if used concomitantly with a proton pump inhibitor.

Selpercatinib has pH-dependent solubility, with decreased solubility at higher pH and should therefore be administered 2 hours before concomitant H2 receptor antagonists (see sections 4.2 and 4.5 of the SmPC).

Selpercatinib inhibits the renal transporter multidrug and toxin extrusion protein 1 (MATE1). *In vivo* interactions of selpercatinib with clinically relevant substrates of MATE1, such as creatinine, may occur.

Selpercatinib is a substrate for P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) in vitro, however these transporters do not appear to limit the oral absorption of selpercatinib, as its oral bioavailability is 73% and its exposure was increased minimally by co-administration of the P-gp inhibitor rifampicin.

Selpercatinib is an in vitro inhibitor of P-gp and BCRP. Caution should be used when taking a P-gp substrate (e.g., fexofenadine, dabigatran etexilate, digoxin, colchicine, saxagliptin).

The provided safety exposure-response analyses do not establish clear relationships between the systemic exposures of selpercatinib (doses up to 160 mg BID) and the likelihood of occurrence of the investigated AEs: increase in ALT, AST, hypersensitivity or hypertension. However, it is important to note that the incident rates for each AEs were very low (<15%) to be able to highlight relationships.

2.4.5. Conclusions on clinical pharmacology

Overall, the PK/PD of selpercatinib has been sufficiently characterized in healthy subjects and in the target patients based on formal phase 1 and 2 studies.

2.5. Clinical efficacy

This application is based on a single pivotal study LOXO-RET-17001 (LIBRETTO-001), a multicentre, open-label, multicohort, Phase 1/2 study in patients with advanced solid tumours, including RET fusion-positive solid tumours (e.g., NSCLC, thyroid, pancreas, colorectal), RET-mutant MTC, and other tumours with RET activation (e.g., mutations in other tumour types or other evidence of RET activation).

This study is ongoing and includes two parts: Phase 1 (dose escalation) and Phase 2 (dose expansion); the study is currently in Phase 2. The study schematic is provided below.

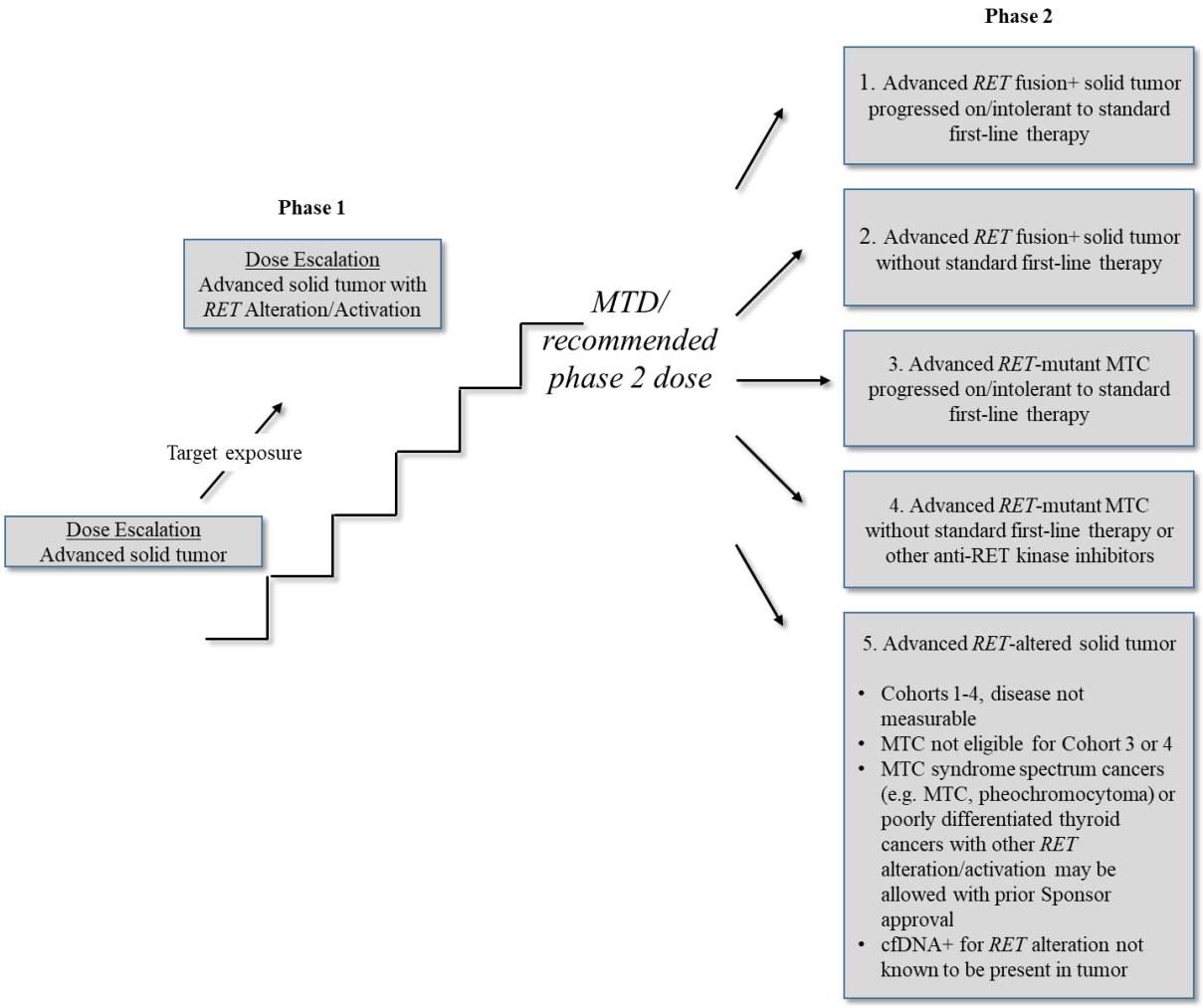


Figure 11. Study schema

2.5.1. Dose response study

LIBRETTO-001 Study

Phase 1 - Dose escalation

Objectives

The primary objective for the study was to determine the MTD/recommended Phase 2 dose (RP2D) of selpercatinib.

Secondary objectives included determination of the safety and tolerability of selpercatinib, characterisation of the PK properties, and assessment of the anti-tumour activity of selpercatinib by determining ORR using RECIST 1.1 or RANO, as appropriate to tumour type.

Design - Methods

This phase is a sequential-cohort dose escalation designed to identify the maximum tolerated dose (MTD) through incidence and characterisation of dose-limiting toxicities (DLT). The study employs a classical 3 + 3 dose escalation design, with 3 or 6 patients enrolled in each dose cohort. The starting dose of LOXO-292 in oral capsule form was 20 mg per day (eg, 20 mg QD). The nine prespecified LOXO-292 dose levels were 20 mg QD, 20 mg BID, 40 mg BID, 60 mg BID, 80 mg BID, 120 mg BID, 160 mg BID, 240 mg BID, 200 mg BID.

In order to be eligible for the assessment of DLT, each patient in a given cohort must have completed safety assessments through Day 28 of Cycle 1 and received at least 75% of the planned total dose in Cycle 1 (unless due to toxicity). The rules for cohort advancement and the definition of the MTD are found in the protocol. Dose advancement was overseen by a Safety Review Committee (SRC). The SRC also periodically reviewed serious adverse events (SAEs) and other safety-related data throughout the conduct of the study. Enrolment in the next dose escalation cohort could begin, with SRC approval:

- If the first 3 patients in the prior dose level cohort had received a minimum of 75% of the planned total dose in Cycle 1(unless due to toxicity) and completed safety assessments through Cycle 1 Day 28 and none had a dose-limiting toxicity (DLT); or
- If 1 of 3 patients within the prior dose level cohort had a DLT, and 3 additional patients had been enrolled and none of the additional 3 patients had a DLT (i.e., 1 of 6 patients had a DLT).

Escalation could proceed through all dose levels or until the SRC and Sponsor determine that a suitable dose has been achieved based on available data (safety, PK exposure, clinical activity).

After completion of the 28-day DLT period in Cycle 1, intrapatient dose escalation was permitted by the Sponsor, provided that the patient is tolerating their current dose and the dose level to which the patient will be escalated has already been evaluated, has a DLT rate of < 33%, and has been declared safe by the SRC.

During the dose escalation phase, selected cohorts previously declared safe by the SRC may be expanded to a total of approximately 15 patients to further investigate the tolerability, PK and biological activity of LOXO-292. These additional patients will have confirmed RET status, and priority will be given to patients with RET alterations. During Phase 1, enrolment of patients to the current dose cohort under evaluation will take precedence. The SRC will continue to monitor the cumulative safety data from the cohorts previously declared safe and the current dose cohort under evaluation.

Patients consented on protocol version 4.0 or earlier could be enrolled in Phase 1 dose expansion cohorts based on tumour type and prior exposure to tyrosine kinase inhibitors with anti-RET activity as specified below:

1. Cohort 1: RET-fusion NSCLC previously treated with kinase inhibitor(s) with anti-RET activity
2. Cohort 2: RET-fusion NSCLC with no prior treatment with kinase inhibitor(s) with anti- RET activity
3. Cohort 3: RET-mutant MTC previously treated with kinase inhibitor(s) with anti-RET activity
4. Cohort 4: RET-mutant MTC with no prior treatment with kinase inhibitor(s) with anti- RET activity
5. Cohort 5:
   - evaluable but nonmeasurable disease
   - other tumour type (not NSCLC or MTC)
   - other *RET* gene alteration (excluding synonymous, frameshift, or nonsense mutations) or other evidence of increased RET activity
   - circulating free DNA (cfDNA) positive for a *RET* gene alteration with tumour discordant or unknown and not further evaluable
   - RET mutation-negative MTC.

This study established 160 mg BID as the recommended Phase 2 dose, with 496 of the 531 enrolled patients (93.4%) patients receiving at least one selpercatinib dose of 160 mg BID. There was 1 DLT among 439 patients who received 160 mg BID. The SRC determined to initiate enrolment to dose expansion (Phase 2) at a dose of 160 mg BID. The recommended Phase 2 dose was selected based on a favourable safety profile, PK analyses consistent with level of target engagement as predicted by preclinical models, and promising and durable anti-tumour activity at 160 mg BID.

2.5.2. Main study

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, LOXO-RET-17001)

Phase 2 - Dose Expansion

The study is currently ongoing and continuing to enrol up to ~750 patients with advanced solid tumours with evidence of a RET gene alteration in tumour and/or blood (e.g., gene fusions and/or mutations, excluding synonymous, frame shift, or nonsense mutations).

Patients were planned to be enrolled to one of 5 Phase 2 cohorts to better characterize the safety and efficacy of selpercatinib in patients with specific abnormalities in RET. These cohorts were different from the expansion cohorts of the Phase I and defined a larger population; the type of RET alteration, the type of disease (solid vs MTC), and the number of previous treatments received were taken into account.

Table 15. Phase 2 Cohorts in LIBRETTO-001

Phase 2 Cohorts	
Cohort 1	*RET* fusion-positive solid tumour progressed on or intolerant to ≥ 1 prior standard first-line therapy
Cohort 2	*RET* fusion-positive solid tumour without prior standard first-line therapy
Cohort 3	*RET*-mutant MTC progressed on or intolerant to ≥ 1 prior standard first-line cabozantinib and/or vandetanib
Cohort 4	*RET*-mutant MTC without prior standard first-line cabozantinib or vandetanib or other kinase inhibitors(s) with anti-RET activity
Cohort 5	• Cohorts 1-4 without measurable disease; • MTC not eligible for Cohorts 3 or 4; • MTC syndrome spectrum cancers (e.g., MTC, pheochromocytoma) or poorly differentiated thyroid cancers with other *RET*-alteration/activation (allowed with Sponsor approval); • cfDNA positive for a *RET* gene alteration not known to be present in a tumour sample.

For Cohorts 1 through 4, evidence of a RET gene alteration in tumour (i.e., not just blood) as defined in Table below, was required (a positive germline test for a RET mutation was acceptable for patients with MTC).

Table 16. Definition of RET Alterations

***RET* mutation**[a]
Previously reported activating *RET* gene mutation excluding synonymous, frameshift, or nonsense mutations. For MTC, *RET* gene mutation not known to be activating, negative, or unknown could be enrolled during Phase 1, and with Sponsor approval, to Cohort 5 of Phase 2.
***RET* fusion**[a]

By PCR or NGS (FISH as the only molecular result was acceptable for Phase 1 dose escalation and Cohort 5 but not Cohorts 1 and 2 of Phase 2 [dose expansion]).
***RET* mutation[a] or *RET* fusion[a]**
Phase 2: no other known validated driver alteration(s) [b].

a According to laboratory with CLIA, ISO/IEC, CAP, or similar certification, so long as a written Molecular Pathology Report is available and clearly asserts the presences of the referenced *RET* alteration.
b Dual driver alterations were only restricted from Cohorts 1 through 4.
Abbreviations: CAP = College of American Pathologists; CLIA = Clinical Laboratory Improvement Amendments; FISH = Fluorescence in Situ Hybridisation; ISO/IEC = International Organization for Standardization/Independent Ethics Committee; MTC = medullary thyroid cancer; NGS = next generation sequencing; PCR = polymerase chain reaction.

The Phase 2 study structure consisted of screening, the treatment period, SFU, and LTFU. An RP2D of 160 mg BID was selected by the SRC during Phase 1 of the study. Cycles were 28 days of continuous BID dosing. Assessments included periodic radiologic evaluation and ongoing safety assessments.

Methods

Study Participants

Main Inclusion Criteria for Phase 1

1. Patients with a locally advanced or metastatic solid tumour who:

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

• no standard therapy exists, or

• in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or

• decline standard therapy.

2. Prior MKIs with anti-*RET* activity are allowed.

3. A *RET* gene alteration is not required initially. Once adequate PK exposure is achieved, evidence of *RET* gene alteration in tumour and/or blood is required (e.g., gene rearrangement and/or mutation, excluding synonymous, frameshift, or nonsense mutations) as identified through molecular assays, as performed for clinical evaluation.

The *RET* alteration result should be generated from a laboratory with Clinical Laboratory Improvement Amendments (CLIA), International Standards (ISO)/IEC, College of American Pathologists (CAP) or other similar certification. The Sponsor should be contacted to discuss test results from laboratories where such certification is not clearly demonstrated to determine eligibility.

Notes:

• During Phase 1, a *RET* gene alteration is not required initially. The Sponsor's preclinical data indicates that a selpercatinib plasma level of 70 ng/mL is equivalent to the IC50 for RET (corrected for human plasma protein binding). Therefore, once a dose level is achieved that: (1) is associated with a DLT rate of < 33%; (2) is deemed safe by the SRC; and (3) is associated with a Cmin of > 70 ng/mL at steady state in ≥ 70% of patients in the same dosing cohort (e.g., 3/3, 3/4, 4/5, 5/6 patients, etc.), enrollment to subsequent dose levels during Phase 1 will be restricted to patients with: (1) RET fusion-positive solid tumours; (2) MTC; (3) an advanced solid tumour that harbors a *RET* gene alteration (excluding synonymous, frameshift, or nonsense mutations); or (4) with prior Sponsor approval, an advanced solid tumour with other evidence of RET activation (refer to Protocol Section 4).

• A positive germline test for a *RET* mutation is acceptable for patients with MTC.

• Local testing in a CLIA, ISO/IEC, CAP, or other similar certified laboratory is sufficient.

• In all cases, an anonymised/redacted Molecular Pathology Report or other report(s) describing tumour *RET* (and other) alteration analysis should be submitted to the Sponsor or designee during/prior to eligibility.

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

5. At least 18 years of age. • For countries and sites where approved, patients as young as 12 years of age may be enrolled.

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

7. Life expectancy of at least 3 months.

8. Archived tumour tissue sample available.

9. Adequate haemtologic status

10. Adequate hepatic function.

11. Adequate renal function.

Inclusion Criteria for Phase 2

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

1. Cohorts 1 and 3: failed or intolerant to standard of care.

   -Cohort 1 (RET fusion-positive solid tumour). NSCLC: platinum-based chemotherapy (or other chemotherapy if not eligible for platinum) or PD-1/PD-L1 immunotherapy or both. Thyroid: sorafenib and/or lenvatinib, patients must also be radioactive iodine-refractory as appropriate

   -Cohort 3 (RET-mutant MTC). Cabozantinib or vandetanib or both agents2. Cohorts 1-4: enrolment will be restricted to patients with evidence of a RET gene alteration in tumour (i.e., not just blood). However, a positive germline DNA test for a RET gene mutation is acceptable in the absence of tumour tissue testing for patients with MTC.

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

3. Cohort 4: radiographic PD within the previous 14 months. Patients otherwise eligible for cohort 4 who do not demonstrate radiographic PD within the previous 14 months may be enrolled to cohort 5 if a compelling rationale is provided by the investigator and approved by the Sponsor.

Main Exclusion Criteria for Phase 1 and Phase 2

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

2. Prior treatment with a selective RET inhibitor(s).

3. Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment, with the exception of patients receiving radiation to more than 30% of the bone marrow or

with a wide field of radiation, which must be completed at least 4 weeks prior to the first dose of study treatment.

4. Symptomatic primary CNS tumour, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. **Exception:** Patients are eligible if neurological symptoms and CNS imaging are stable and steroid dose is stable for 14 days prior to the first dose of selpercatinib and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery (SRS).

Note: During the Phase 2 portion of the study, all prior local treatments for CNS disease (e.g., surgery, whole brain radiation, SRS), the start and stop dates for each prior local therapy, the specific lesions treated (if SRS and/or surgery), whether the patient developed intracranial progression after the last prior local treatment, and which lesions progressed since completion of the local therapy must be documented.

5. Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of selpercatinib or prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF) interval > 470 msec on at least 2/3 consecutive electrocardiograms (ECGs) and mean QTcF > 470 msec on all 3 ECGs during Screening. Correction of suspected drug-induced QTcF prolongation may be attempted at the Investigator's discretion if clinically safe to do so.

6. Uncontrolled symptomatic hyperthyroidism or hypothyroidism.

7. Uncontrolled symptomatic hypercalcemia or hypocalcemia.

8. Current treatment with certain strong CYP3A4 inhibitors or inducers.

9. Current treatment with proton pump inhibitors (PPIs). **Note:** Treatment with PPIs must be stopped 1 or more weeks prior to the first dose of selpercatinib.

Treatments

There were two study periods:

- Dose Escalation Phase (Phase 1): Patients receive selpercatinib dose levels that ranged from 20 mg QD to 240 mg BID.
- Dose Expansion Phase (Phase 2): Patients received selpercatinib 160 mg BID.

Individual patients continued selpercatinib dosing 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.

Throughout the conduct of the selpercatinib clinical development programme, investigational product was available in capsule form with selpercatinib simple blend or in powder and a solution form (liquid suspension).

Dosing followed a fixed milligram format (as opposed to weight-based or BSA-based). Dosing for an individual was to be at a consistent time each day and BID dosing was to be separated by approximately 12 hours; a minimum time period of 6 hours was required between consecutive doses. Doses that were late by more than 6 hours were to be skipped and recorded in the dosing diary as missed.

Through Protocol v7.0, patients were not to consume food for at least 2 hours before and for at least 1 hour after the dose of selpercatinib; after the data cut-off date, the protocol was amended to note that selpercatinib could be given with or without food based on a food effect study in healthy volunteers indicating that the effect of food on selpercatinib bioavailability was minimal.

Objectives

The primary objective of Phase 2 was to assess, for each Phase 2 expansion cohort, the antitumour activity of LOXO-292 by determining ORR using RECIST 1.1 or RANO, as appropriate for the tumour type.

Secondary objectives of Phase 2 included other efficacy parameters, as best change in tumour size from baseline, duration of response (DOR), central nervous system (CNS) ORR, CNS DOR, time to any and best response, and clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS). Determination of the safety and tolerability of selpercatinib, and characterisation of the PK properties were also included.

Exploratory objectives included determination of the relationship between PK and drug effects (including efficacy and safety), evaluations of serum tumour markers, carcinoembryonic antigen (CEA) and calcitonin (medullary thyroid cancer [MTC]), thyroglobulin (for patients with non-MTC thyroid cancer), and adrenocorticotropic hormone (ACTH)/cortisol (for patients with Cushing's disease related to their cancer), before, during, and at the end of treatment with selpercatinib. Additional exploratory objectives include characterisation of *RET* gene fusions and mutations and concurrently activated oncogenic pathways by molecular assays, including next-generation sequencing (NGS) from tumour biopsies and circulating cell-free DNA (cfDNA), and collection of patient-reported outcomes (PROs) data to explore disease-related symptoms and health-related quality of life (HRQoL).

Outcomes/endpoints

Primary endpoint:

Objective response rate (ORR) by IRC assessment. ORR was defined as the proportion of patients with BOR of confirmed CR or confirmed PR based on RECIST v1.1. BOR was defined as the best response designation for each patient recorded between the date of the first dose of selpercatinib and the data cut-off of 17 June 2019, or the date of documented disease progression per RECIST v1.1 or the date of subsequent therapy or cancer-related surgery.

Secondary endpoints:

- ORR based on investigator assessment using RECIST v1.1;

- Time to response (TTR);

- Time to best response (TTBR);

- Duration of response (DOR);

- Clinical benefit rate (CBR), calculated as the proportion of patients reaching CR, PR, or stable disease lasting 16 or more weeks;

- Progression-free survival (PFS);

- Overall survival (OS);

- CNS ORR and CNS DOR.

IRC assessment provided the principal data for all analysis sets, while investigator assessments were considered supportive data for all analysis sets.

Sample size

Phase 2:

For Cohort 1 (patients with *RET* fusion-positive solid tumours who progressed on or were intolerant to standard first-line therapy for their cancers), a true ORR of ≥ 50% was hypothesised when selpercatinib was administered to patients with such malignancies. A sample size of 55 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial confidence interval (CI) about the estimated ORR that exceeds 30%. Ruling out a lower limit of 30% was considered clinically meaningful and consistent with the estimated response rates seen with approved targeted therapies in molecularly defined patient populations who have failed prior therapies (e.g., osimertinib, crizotinib, alectinib, and others).

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

For Cohort 3 (patients with *RET*-mutant MTC who progressed on or were intolerant to vandetanib and/or cabozantinib), a true ORR of ≥ 35% was hypothesised when selpercatinib was administered to such patients. A sample size of 83 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 20%. Ruling out a lower limit of 20% was considered clinically meaningful in patients who have failed prior MKI therapy (e.g., cabozantinib) and currently have limited treatment options for their advancing disease.

For Cohort 4 (patients with *RET*-mutant MTC who are MKI-naïve), a true ORR of ≥ 50% was hypothesised when selpercatinib was administered to such patients. A sample size of 55 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 30%.

Notwithstanding the statistical considerations above, if approved by the Safety Review Committee (SRC), enrolment beyond the above sample sizes in each of Cohorts 1 through 5, was allowed, in order to accommodate enrolment demand and allow for the characterisation of AEs that may occur with low frequency. With a sample size of 150 patients, the probability of observing one or more instances of a specific AE within a cohort with a true incidence rate of 1% and 2% was 77.9% and 95.2%, respectively. Up to ~150 patients in Cohort 1 would be allowed to accommodate enrolment of other *RET* fusion-positive solid tumours.

Randomisation

LIBRETTO-001 study was a non-randomised study.

Blinding (masking)

LIBRETTO-001 study was a single-arm study.

Statistical methods

The protocol (Original Version) was dated 01 March 2017. Prior to data cut-off (DCO), there were 7 versions of the protocol that included subversions depending on the geographical location.

Major changes in the conduct of the study were performed by Protocol version 5.0 dated 30 May 2018 that updated the trial design from a two-part Phase 1 (dose escalation and dose expansion) study to a Phase 1/Phase 2 study based on promising early evidence from ongoing Phase I of durable antitumour activity in patients with RET-altered cancers; RP2D of 160 mg BID was selected, modifications were made to the composition of the cohorts, planned statistical analyses were updated as a reflection of the changes. In addition, it added assessment of HRQoL with validated instruments, included a new liquid formulation of selpercatinib for patients who cannot swallow capsules and included assessment of tumour serum thyroglobulin levels for patients with non-MTC thyroid cancers.

Analysis Sets

In order to facilitate regulatory review of the LOXO-RET-17001 data in support of the proposed indications for marketing authorisation, the applicant has created data sets that are distinctive from those discussed in the clinical study report.

The basis of the data supporting the MAA is primarily on an analysis of efficacy and safety data from patients enrolled into LOXO-RET-17001, as of 17 June 2019. The dataset includes 531 patients who have been treated with selpercatinib, 439 of whom were treated at the recommended Phase 2 dose (RP2D) of 160 mg BID.

Specifically, these data sets were categorised into broad groupings of patients with RET fusion- positive NSCLC, RET-mutant MTC, and RET fusion-positive thyroid cancer. These groupings then formed the basis for defining primary analysis sets (PAS) in NSCLC and MTC, which specifically included patients who received prior platinum-based chemotherapy (in the case of NSCLC) or prior cabozantinib or vandetanib (in the case of MTC). The PAS data sets also met specific criteria in terms of a minimum follow-up duration of 6 months from first dose, and statistical considerations which led to the sample sizes of 105 and 55 patients for the NSCLC and MTC PAS, respectively. The majority of patients in the PAS received at least 1dose of selpercatinib at the recommended dose of 160 mg twice daily (BID). The PAS data sets, together with supplemental analysis sets (SAS) of patients in the first-line treatment setting, and a supportive analysis set of RET fusion- positive thyroid cancer patients, deliver the evidence base for the proposed indications.

It should be noted that results from Phase 1 of study LIBRETTO-001 were submitted to ASCO in April 2018, prior to submission of the May 2018 Briefing Book, and disclosed in June 2018 based on an interim analysis of data from investigator assessment of responses in the first 25 RET fusion-positive NSCLC and 19 *RET*-mutant MTC patients enrolled. Although the disclosure of preliminary efficacy did not represent the PAS defined for registration, the absence of confirmatory testing criteria prior to this analysis and disclosure may introduce bias, as discussed with the CHMP in July 2019. Therefore, sensitivity analysis was performed on a modified NSCLC & MTC PAS, which excludes the initial 25 and 19 patients who were enrolled and included in the ASCO disclosure, but includes the 25 and 19 patients enrolled subsequent to the initial 105 & 55, to maintain an overall sample size of 105 &55 for the modified PAS.

For *RET* fusion-positive NSCLC, the analysis sets include a PAS, integrated analysis set (IAS) and 3 supplemental analysis sets (SAS): the PAS and SAS1 primarily support the indication for *advanced RET fusion-positive NSCLC in patients who require systemic therapy*.

Table 17. Description of Analysis Sets for RET Fusion-Positive NSCLC of LIBRETTO-001.

Analysis Set	Analysis Set Description
PAS (Primary Analysis Set)	The first 105 *RET* fusion-positive NSCLC patients enrolled in Phase 1 and Phase 2 who met the following criteria: 1. Evidence of a protocol-defined qualifying and definitive *RET* fusion, prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US)

Analysis Set	Analysis Set Description	
	molecular pathology report. Patients with a *RET* fusion co-occurring with another putative oncogenic driver, as determined at the time of study enrolment by local testing, were included. 2. Measurable disease[1] by RECIST v1.1 by investigator assessment. 3. Received 1 or more lines of prior platinum-based chemotherapy. 4. Received 1 or more doses of selpercatinib.	
IAS (Integrated Analysis Set)	• All *RET* fusion-positive NSCLC patients treated in LIBRETTO-001 by the data cut-off date who met PAS criteria 1-4. • Included all PAS patients and those enrolled after the 105th patient but on or before the data cut-off.	
SASs (Supplemental Analysis Sets)	• All other *RET* fusion-positive NSCLC patients (e.g., not part of the PAS/IAS) who were treated in LIBRETTO-001 as of the data cut-off date • SAS1 and SAS2: met PAS criteria 1, 2 and 4 • SAS3: met PAS criteria 1 and 4 • SAS assignment was nonoverlapping, thus SAS1-3 are mutually exclusive with each other	**SAS1 (Treatment Naive)** • No prior systemic therapy **SAS2 (Prior Other Systemic Therapy)** • Received prior systemic therapy other than platinum-based chemotherapy **SAS3 (Non-measurable Disease)** • No measurable disease[2]
Additional Analysis Sets	*RET* fusion-positive thyroid cancers, met PAS criteria 1 and 4	
	RET fusion-positive tumours other than NSCLC and thyroid, met PAS criteria 1 and 4	
CNS Response Analysis Sets	All treated *RET* fusion-positive patients who met PAS criteria 1 and 4 and had investigator-assessed CNS metastases at baseline (reported as target or non-target lesion per RECIST v1.1). These patients are described in the following 3 subsets:	CNS response in the PAS CNS response in all patients with *RET* fusion-positive NSCLC CNS response in patients with *RET* fusion-positive thyroid cancer or *RET* fusion-positive other tumours
Post-hoc Sensitivity PAS subset	Subset of patients from the PAS, which excludes the initial 25 patients who were enrolled and included in the June 2018 ASCO disclosure (modified NSCLC PAS).	
TOTAL LIBRETTO-001 PATIENTS INCLUDED IN THIS NSCLC SCE[3]		

[1] Patients without measurable disease who were enrolled in Phase 1 dose escalation were included in the PAS. Refer to the NSCLC SAP for details.
[2] Patients without measurable disease who were enrolled into Phase 1 dose expansion Cohort 5 (per protocol version 4.0 or earlier) or Phase 2 Cohort 5 (per protocol version 5.0 and later).
[3] Total patients in this NSCLC SCE is the sum of IAS, SAS1, SAS2, SAS3, *RET* fusion-positive Thyroid Cancer, and *RET* fusion-positive Other Tumours.

The *RET fusion-positive thyroid cancer* patients were included as a supportive analysis set (n=27) and primarily support the indication for *advanced RET fusion-positive thyroid cancer in patients who require systemic therapy and who have progressed following prior therapy*. The patient population is derived from Phase 1 and Phase 2 cohort 1. Efficacy and safety results support second-line treatment and greater.

For *RET*-mutant MTC, the analysis sets include a PAS, IAS and 2 supplemental analysis sets (SAS1 & SAS2). The PAS and SAS1 primarily support the indication for *advanced RET-mutant MTC in patients who require systemic therapy*.

Table 18. Description of Analysis Sets Ret-Mutant MTC of LIBRETTO-001.

	Analysis Set Description
PAS (Primary Analysis Set)	The first 55 *RET*-mutant MTC patients enrolled in Phase 1 and Phase 2 who met the following criteria: 1. Evidence of a protocol-defined qualifying and definitive *RET* mutation prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with a *RET* mutation co-occurring with another oncogenic driver, as determined at the time of study enrolment by local testing, were included. 2. Measurable disease[1] by RECIST v1.1 by investigator assessment.

	Analysis Set Description	
	3. Received 1 or more lines of prior therapy of cabozantinib or vandetanib. 4. Received 1 or more doses of selpercatinib.	
IAS **(Integrated Analysis Set)**	• All *RET*-mutant MTC patients treated in LIBRETTO-001 by the data cut-off date who met PAS criteria 1-4. • Included all PAS patients and those enrolled after the 55th patient but on or before the data cut-off.	
SASs **Supplemental Analysis Sets**	• All other *RET*-mutant MTC patients (e.g., not part of the PAS/IAS) who were treated in LIBRETTO-001 as of the data cut-off date • SAS1: met PAS criteria 1, 2, and 4 • SAS2: met PAS criteria 1 and 4 • SAS assignment was nonoverlapping, thus SAS1-2 are mutually exclusive with each other	**SAS1 (Cabozantinib and Vandetanib Naive)** • Could have received therapies other than cabozantinib or vandetanib **SAS2 (Non-measurable disease)** • No measurable disease[2]
Additional Analysis Set	*RET* fusion-positive thyroid cancers, met PAS criteria of protocol-defined qualifying and definitive *RET* fusion, prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report and received 1 or more doses of selpercatinib	
Post hoc sensitivity analysis set	Subset of patients in the PAS which excludes the initial 19 patients who were enrolled and included in the ASCO disclosure, and includes the 55 patients continuously enrolled after the April 2018 ASCO cut-off to maintain an overall sample size of 55 (modified MTC PAS).	
RET-mutant MTC patients post MKI	Patients with RET-mutant MTC who have progressed after prior cabozantinib or vandetanib (MKI-progressive MTC PAS).	
Total LIBRETTO-001 patients included in this MTC SCE[3]		

[1] Patients without measurable disease who were enrolled in Phase 1 dose escalation were included in the PAS. Refer to the MTC SAP for details.
[2] Patients without measurable disease who were enrolled into Phase 1 dose expansion Cohort 5 (per protocol version 4.0 or earlier) or Phase 2 Cohort 5 (per protocol version 5.0 and later).
[3] Total patients in this MTC SCE is the sum of IAS, SAS1, SAS2 and *RET* fusion-positive thyroid cancer.

Sample Size Considerations

NSCLC - For the PAS, the SAP hypothesized that a true ORR of ≥ 50% would indicate significant clinical benefit in patients with *RET* fusion-positive NSCLC who had progressed on or after treatment with platinum-based chemotherapy. Under this assumption, a sample size of 105 patients was estimated to provide more than 98% power to rule out 30% as the lower boundary of a 2-sided 95% exact binomial CI for the ORR. The applicant considered this boundary as clinically meaningful given the limited treatment options in the referenced disease setting. Under the primary analysis, the lower limit of the 95% CI would exceed 30% when the observed ORR was 40% or greater (Clopper-Pearson method).

MTC - For the PAS, the SAP hypothesized that a true ORR of ≥ 40% would indicate significant clinical benefit in patients with RET-mutant MTC who had progressed on or after treatment with cabozantinib or vandetanib. Under this assumption, a sample size of 55 patients was estimated to provide 89% power to rule out 20% as the lower boundary of a 2-sided 95% exact binomial CI for the ORR. The applicant considered this boundary as considered clinically meaningful given the limited treatment options in the referenced disease setting. Under the primary analysis, the lower limit of the 95% CI would exceed 20% when the observed ORR was 33% or greater (Clopper-Pearson method).

TC – No former hypothesis was settled for RET- fusion positive TC.

As already discussed with the applicant as part of Scientific Advice procedures (EMA/CHMP/SAWP/398728/2019 & EMA/CHMP/SAWP/398729/2019), and for the NSCLC and MTC PAS, respectively, no confirmatory testing was pre-specified in this study and the current ORR is based on a

substantial part of the proposed number of patients for the PAS that were not pre-defined but are subpopulations of the overall population of the open-label study LOXO-RET-17001. Results and analysis sets are defined post hoc.

Results

As of the 17 June 2019 data cut-off, 531 patients had been treated on LIBRETTO-001 (439 of whom were treated at the recommended Phase 2 dose (RP2D) of 160 mg BID), including 226 patients with RET-mutant MTC, 253 patients with RET fusion-positive NSCLC, 27 patients with RET fusion-positive thyroid cancer and 11 patients with RET fusion-positive other tumours.

All 531 patients were included in the Safety Analysis Set at the initial submission. At the initial DCO, 304 patients (57.3%) were eligible for response analysis whereas all 531 patients enrolled had an opportunity to be followed for at least 6 months from first dose of selpercatinib at the later DCO date of 16 December 2019.

RET alterations were documented in 525 (98.9%) of the 531 patients; this included all patients (100%) in Cohorts 1 through 4 and 94.8% of patients in Cohort 5, as was expected based on the enrollment requirements for the specific cohorts.

Participant flow

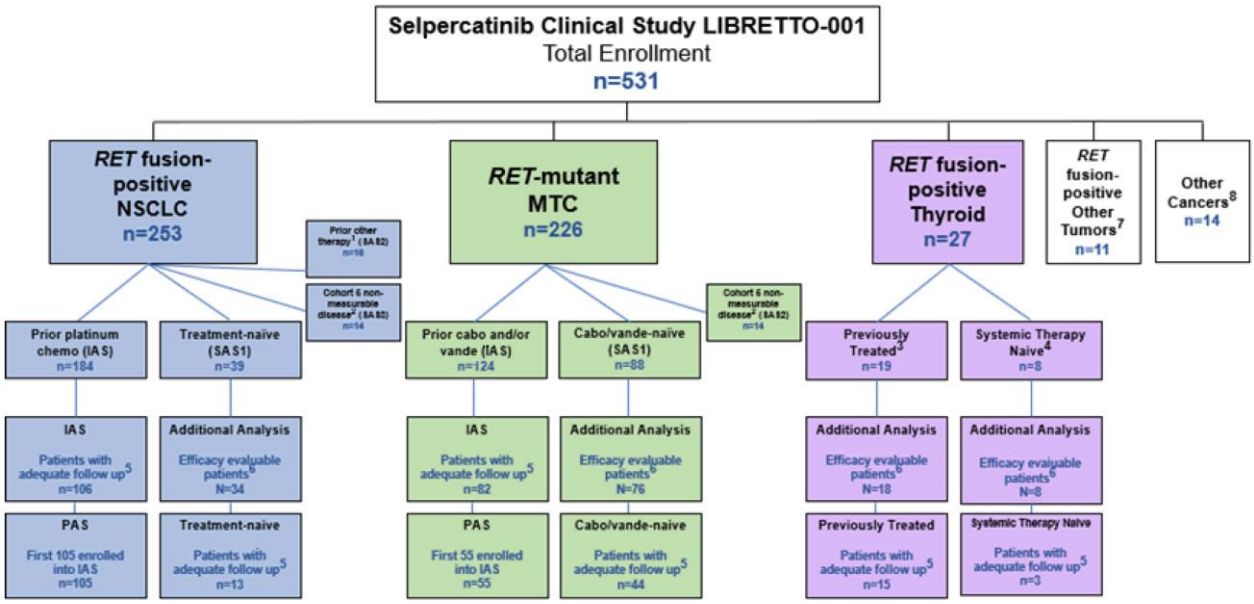


Figure 12. Selpercatinib Enrolment and Analysis Populations

Recruitment

The study was initiated on 09 May 2017 and is ongoing (cut-off for interim analysis: 17 June 2019 and 16 December 2019). Patients were enrolled at 89 centres in the countries of Australia, Canada, Denmark, Germany, Japan, Hong Kong, Israel, Singapore, France, Italy, Spain, South Korea, Switzerland, Taiwan, United Kingdom and the US as of 30 Mar 2020.

Conduct of the study

Protocol amendments

The protocol versions that were implemented and enrolled patients before the data cut-off date for this interim CSR included Protocol versions 1.0 through 7.0 (and subversions of versions 1.0 through 7.0) as listed in Table 19.

Phase 2 cohorts enrolled patients beginning with protocol version 5.0 (through version 7.0).

Table 19.:Protocol Versions and Dates

Protocol Version	Date	Country
Original Protocol Version 1.0 – Not implemented	01 March 2017	United States
Version 2.0	27 March 2017	United States
Version 3.0	20 July 2017	United States
Version 4.0	21 November 2017	United States
Version 4.5	11 April 2018	Japan
Version 5.0	30 May 2018	United States
Version 5.1	15 June 2018	Europe
Version 6.0	11 September 2018	United States
Version 6.1	11 September 2018	Europe
Version 7.0	18 October 2018	United States
Version 7.1	18 October 2018	Canada and Europe
Version 7.2	18 October 2018	Japan
Version 7.3	26 December 2018	Denmark
Version 7.4	15 March 2019	Germany

Protocol deviations

Important protocol deviations were reported in 40 (7.5%) patients. The most frequently reported important protocol deviations were those relating to investigational product in 17 patients, and Inclusion Criteria and SAE reporting, each in 8 patients. None of the protocol deviations were considered to have an effect on the safety or efficacy outcomes of the study.

The following sections will present the results by applied indication:

RET fusion-positive NSCLC

A total of 253 RET fusion-positive NSCLC patients were enrolled and treated in LIBRETTO-001 study.

From the total NSCLC population, the majority of the patients were still on treatment (68.0%), at the time of the December 2019 DCO (approximately 31 months after the first patient was enrolled). Generally, the main cause of treatment discontinuation was disease progression. Around 20.9% of the total NSCLC patients continued treatment with selpercatinib after progression. The main cause of study discontinuation was death; figures were of 21.9% and 2.6% in the PAS and SAS1 population, respectively.

Table 20. Patient Disposition (RET Fusion-positive NSCLC) - 16 December 2019 Data cut-off

	PAS (a subset of IAS)	IAS Prior Platinum Chemo	SAS1 Treatment-naïve	SAS2 Prior Other Systemic Therapy	SAS3 Non-measurable Disease	Total
Treated	105	184	39	16	14	253
Treatment ongoing, n (%)	63 (60.0)	125 (67.9)	30 (76.9)	8 (50.0)	9 (64.3)	172 (68.0)
Treatment discontinued, n (%)	42 (40.0)	59 (32.1)	9 (23.1)	8 (50.0)	5 (35.7)	81 (32.0)
Disease progression	25 (23.8)	34 (18.5)	6 (15.4)	6 (37.5)	4 (28.6)	50 (19.8)
Adverse event	5 (4.8)	11 (6.0)	2 (5.1)	0	1 (7.1)	14 (5.5)
Withdrawal of consent	6 (5.7)	7 (3.8)	0	0	0	7 (2.8)
Death	2 (1.9)	3 (1.6)	1 (2.6)	2 (12.5)	0	6 (2.4)
Other	4 (3.8)	4 (2.2)	0	0	0	4 (1.6)
Treatment continued post-progression, n (%)	33 (31.4)	42 (22.8)	5 (12.8)	5 (31.3)	1 (7.1)	53 (20.9)
Study status continuing, n (%)	70 (66.7)	138 (75.0)	37 (94.9)	10 (62.5)	10 (71.4)	195 (77.1)
Study status discontinued, n (%)	35 (33.3)	46 (25.0)	2 (5.1)	6 (37.5)	4 (28.6)	58 (22.9)
Withdrawal of consent	12 (11.4)	16 (8.7)	1 (2.6)	1 (6.3)	2 (14.3)	20 (7.9)
Death	23 (21.9)	30 (16.3)	1 (2.6)	5 (31.3)	2 (14.3)	38 (15.0)

Analysis set definitions: PAS = Primary Analysis Set; IAS = Prior Platinum Chemotherapy; SAS1 = Treatment-naïve; SAS2 = Prior Other Systemic Therapy; SAS3 = Non-measurable Disease. Note: For *RET* fusion-positive NSCLC, the PAS includes the first 105 patients of the IAS. The Total column is the sum of the IAS, SAS1, SAS2, and SAS3.

Baseline data

The median age is 61 years old for the total NSLC population; with a range between 23 and 86 years old.

Table 21. Summary of demographics

	***RET* Fusion-positive NSCLC**						***RET* fusion-positive Thyroid N = 27**	***RET* fusion-positive Other Tumours N = 11**
	PAS (a subset of IAS) N = 105	**IAS Prior Platinum Chemo N = 184**	SAS1 Treatment-naïve N = 39	**SAS2 Prior Other Systemic Therapy N = 16**	**SAS3 Non-measurable Disease N = 14**	**Total N = 253**		
Age, years								
Median	61.0	62.0	61.0	58.5	60.0	61.0	54.0	54.0
Range	23-81	23-81	23-86	47-71	44-80	23-86	20-88	31-76
Overall age group, n (%)								
18-44 years	17 (16.2)	26 (14.1)	4 (10.3)	0	1 (7.1)	31 (12.3)	7 (25.9)	4 (36.4)
45-64 years	52 (49.5)	89 (48.4)	18 (46.2)	12 (75.0)	7 (50.0)	126 (49.8)	11 (40.7)	4 (36.4)
65-74 years	30 (28.6)	54 (29.3)	13 (33.3)	4 (25.0)	5 (35.7)	76 (30.0)	5 (18.5)	2 (18.2)
≥ 75 years	6 (5.7)	15 (8.2)	4 (10.3)	0	1 (7.1)	20 (7.9)	4 (14.8)	1 (9.1)
Sex, n (%)								
Male	43 (41.0)	79 (42.9)	17 (43.6)	6 (37.5)	6 (42.9)	108 (42.7)	14 (51.9)	8 (72.7)
Female	62 (59.0)	105 (57.1)	22 (56.4)	10 (62.5)	8 (57.1)	145 (57.3)	13 (48.1)	3 (27.3)
Race, n (%)								
White	55 (52.4)	86 (46.7)	28 (71.8)	11 (68.8)	5 (35.7)	130 (51.4)	20 (74.1)	10 (90.9)
Black	5 (4.8)	9 (4.9)	3 (7.7)	0	0	12 (4.7)	1 (3.7)	0
Asian	40 (38.1)	82 (44.6)	7 (17.9)	5 (31.3)	9 (64.3)	103 (40.7)	2 (7.4)	0
Other/Missing	5 (4.8)	7 (3.8)	1 (2.6)	0	0	8 (3.2)	4 (14.8)	1 (9.1)
Baseline ECOG, n (%)								
0	31 (29.5)	66 (35.9)	19 (48.7)	3 (18.8)	6 (42.9)	94 (37.2)	8 (29.6)	3 (27.3)
1	72 (68.6)	114 (62.0)	20 (51.3)	12 (75.0)	8 (57.1)	154 (60.9)	16 (59.3)	7 (63.6)
2	2 (1.9)	4 (2.2)	0	1 (6.3)	0	5 (2.0)	3 (11.1)	1 (9.1)
Smoking history, n (%)								
Never smoked	75 (71.4)	125 (67.9)	29 (74.4)	11 (68.8)	11 (78.6)	176 (69.6)	21 (77.8)	8 (72.7)
Former smoker	29 (27.6)	55 (29.9)	9 (23.1)	5 (31.3)	3 (21.4)	72 (28.5)	6 (22.2)	2 (18.2)
Current smoker	1 (1.0)	4 (2.2)	1 (2.6)	0	0	5 (2.0)	0	0
Missing	0	0	0	0	0	0	0	1 (9.1)

Note: For *RET* fusion-positive NSCLC, the PAS includes the first 105 patients of the IAS. The Total column is the sum of the IAS, SAS1, SAS2, and SAS3.

Table 22: Summary of Baseline Disease Characteristics

	***RET* fusion-positive NSCLC**						***RET* fusion-positive Thyroid N = 27**	***RET* fusion-positive Other Tumours N = 11**
	PAS (a subset of IAS) N = 105	**IAS Prior Platinum Chemo N = 184**	**SAS1 Treatment-naïve N = 39**	**SAS2 Prior Other Systemic Therapy N = 16**	**SAS3 Non-measurable Disease N = 14**	**Total N = 253**		
Primary tumour type, n (%)								
NSCLC	105 (100)	184 (100)	39 (100)	16 (100)	14 (100)	253 (100)	0	0

	***RET* fusion-positive NSCLC**							
	PAS (a subset of IAS) N = 105	**IAS Prior Platinum Chemo N = 184**	**SAS1 Treatment-naïve N = 39**	**SAS2 Prior Other Systemic Therapy N = 16**	**SAS3 Non-measurable Disease N = 14**	**Total N = 253**	***RET* fusion-positive Thyroid N = 27**	***RET* fusion-positive Other Tumours N = 11**
Stage at diagnosis, n (%)								
I, IA, IB	1 (1.0)	2 (1.1)	0	1 (6.3)	1 (7.1)	4 (1.6)	0	0
II, IIA, IIB	0	2 (1.1)	1 (2.6)	1 (6.3)	2 (14.2)	6 (2.4)	1 (3.7)	0
IIIA, IIIB	3 (2.9)	10 (5.4)	0	0	0	10 (4.0)	0	0
IV	84 (80.0)	121 (65.8)	32 (82.1)	10 (62.5)	8 (57.1)	171 (67.6)	16 (59.3)	7 (63.6)
IVA	9 (8.6)	18 (9.8)	2 (5.1)	1 (6.3)	1 (7.1)	22 (8.7)	0	1 (9.1)
IVB	4 (3.8)	18 (9.8)	2 (5.1)	1 (6.3)	2 (14.3)	23 (9.1)	1 (3.7)	0
IVC	4 (3.8)	13 (7.1)	1 (2.6)	2 (12.5)	0	16 (6.3)	8 (29.6)	2 (18.2)
Missing	0	0	1 (2.6)	0	0	1 (0.4)	1 (3.7)	1 (9.1)
Time from diagnosis, months								
Median	30.10	24.20	2.00	7.15	19.50	18.40	92.30	17.40
Range	1.5-142.3	1.5-164.8	0.7-8.1	2.0-112.5	7.4-223.7	0.7-223.7	2.6-401.7	4.1-74.2
History of metastatic disease, n (%)								
Yes	103 (98.1)	179 (97.3)	39 (100)	16 (100)	14 (100)	248 (98.0)	27 (100)	11 (100)
No	2 (1.9)	5 (2.7)	0	0	0	5 (2.0)	0	0
Time from diagnosis of metastatic disease, months								
Median	20.40	19.50	1.60	7.15	10.65	12.50	53.10	4.90
Range	1.5-100.8	1.0-108.1	0.0-8.1	2.0-75.5	0.4-91.1	0-108.1	1.9-344.9	3.0-74.2
At least 1 measurable lesion by investigator, n (%)								
Yes	104 (99.0)	183 (99.5)	39 (100)	16 (100)	0	238 (94.1)	26 (96.3)	9 (81.8)
No	1 (1.0)	1 (0.5)	0	0	14 (100)	15 (5.9)	1 (3.7)	2 (18.2)
Sum of diameters at baseline by investigator, mm								
Median	60.0	54.7	70.0	78.0	0	57.6	54.0	90.0
Range	10.2-248.2	10.0-297.0	15.0-191.0	20.0-249.6	0-0	10.0-297.0	11.0-156.4	26.0-229.0
CNS metastases at baseline by investigator, n (%)								
Yes	37 (35.2)	60 (32.6)	7 (17.9)	10 (62.5)	2 (14.3)	79 (31.2)	7 (25.9)	3 (27.3)
No	68 (64.8)	124 (67.4)	32 (82.1)	6 (37.5)	12 (85.7)	174 (68.8)	20 (74.1)	8 (72.7)

The majority of the patients were diagnosed by NGS on tumour; the most common fusion partners were KIF5B, CCDC6 and NCOA4. Mostly, patients did not present other concomitant oncogenic driver mutation.

Table 23. Prior Cancer-Related Treatments

	***RET* fusion-positive NSCLC**						***RET* fusion-positive**	***RET* fusion-positive Other Tumours**
	PAS (a subset of IAS)	**IAS Prior Platinum Chemo**	**SAS1 Treatment-naïve**	**SAS2 Prior Other Systemic Therapy**	**SAS3 Non-measurable Disease**	**Total**		
	N = 105	**N = 184**	**N = 39**	**N = 16**	**N = 14**	**N = 253**	**N = 27**	**N = 11**
Received prior systemic therapy, n (%)								
Yes	105 (100)	184 (100)	0	16 (100)	14 (100)	214 (84.6)	27 (100)	10 (90.9)
No	0	0	39 (100)	0	0	39 (15.4)	0	1 (9.1)
Type of prior systemic therapy, n (%)								
Platinum Chemotherapy	105 (100)	184 (100)	0	0	13 (92.9)	197 (77.9)	1 (3.7)	8 (72.7)
Anti-PD-1/PD-L1 Therapy	58 (55.2)	100 (54.3)	0	10 (62.5)	6 (42.9)	116 (45.8)	3 (11.1)	2 (18.2)
MKI	50 (47.6)	67 (36.4)	0	6 (37.5)	3 (21.4)	76 (30.0)	15 (55.6)	2 (18.2)
Prior systemic regimens, n (%)								
0	0	0	39 (100)	0	0	39 (15.4)	0	1 (9.1)
1-2	46 (43.8)	101 (54.9)	0	14 (87.5)	9 (64.3)	124 (49.0)	11 (40.7)	7 (63.6)
≥ 3	59 (56.2)	83 (45.1)	0	2 (12.5)	5 (35.7)	90 (35.6)	16 (59.3)	3 (27.3)
Number of prior systemic regimens								
Median	3.0	2.0	0	1.0	2.0	2.0	3.0	2.0
Range	1-15	1-15	0	1-5	1-7	0-15	1-7	0-5
Best response to last systemic treatment, n (%)								
Complete response	0	1 (0.5)	0	0	0	1 (0.4)	0	1 (9.1)
Partial response	15 (14.3)	24 (13.0)	0	0	0	24 (9.5)	2 (7.4)	1 (9.1)
Stable disease	37 (35.2)	62 (33.7)	0	2 (12.5)	5 (35.7)	69 (27.3)	7 (25.9)	1 (9.1)
Progression	32 (30.5)	55 (29.9)	0	10 (62.5)	5 (35.7)	70 (27.7)	8 (29.6)	3 (27.3)
Not evaluated	20 (19.0)	40 (21.7)	0	4 (25.0)	4 (28.6)	48 (19.0)	10 (37.0)	4 (36.4)
Unknown	1 (1.0)	2 (1.1)	39 (100)	0	0	41 (16.2)	0	1 (9.1)
Prior radiotherapy, n (%)								
Yes	62 (59.0)	103 (56.0)	11 (28.2)	9 (56.3)	9 (64.3)	132 (52.2)	15 (55.6)	6 (54.5)
No	43 (41.0)	81 (44.0)	28 (71.8)	7 (43.8)	5 (35.7)	121 (47.8)	12 (44.4)	5 (45.5)
Prior cancer related surgery, n (%)								
Yes	50 (47.6)	84 (45.7)	13 (33.3)	9 (56.3)	7 (50.0)	113 (44.7)	25 (92.6)	7 (63.6)
No	55 (52.4)	100 (54.3)	26 (66.7)	7 (43.8)	7 (50.0)	140 (55.3)	2 (7.4)	4 (36.4)

Analysis Set definitions: PAS = Primary Analysis Set; IAS = Prior Platinum Chemotherapy; SAS1 = Treatment-naïve; SAS2 = Prior Other Systemic Therapy; SAS3 = Non-measurable Disease.
Note: For *RET* fusion-positive NSCLC, the PAS includes the first 105 patients of the IAS. The Total column is the sum of the IAS, SAS1, SAS2, and SAS3.

Table 24. Selpercatinib Dose Intensity (16 December 2019 Data cut-off)

	PAS (a subset of IAS) N = 105	IAS Prior Platinum Chemo N = 184	SAS1 Treatment - naïve N = 39	SAS2 Prior Other Systemic Therapy N = 16	SAS3 Non-measurable Disease N = 14	Total N = 253
20 mg QD	4 (3.8)	4 (2.2)	0	0	0	4 (1.6)
20 mg BID	5 (4.8)	5 (2.7)	0	1 (6.3)	0	6 (2.4)
40 mg BID	9 (8.6)	9 (4.9)	0	0	0	9 (3.6)
60 mg BID	3 (2.9)	3 (1.6)	0	2 (12.5)	0	5 (2.0)
80 mg BID	3 (2.9)	3 (1.6)	2 (5.1)	0	0	5 (2.0)
120 mg BID	11 (10.5)	11 (6.0)	0	2 (12.5)	0	13 (5.1)
160 mg BID[1]	69 (65.7)	148 (80.4)	36 (92.3)	10 (62.5)	14 (100)	208 (82.2)
240 mg BID	1 (1.0)	1 (0.5)	1 (2.6)	1 (6.3)	0	3 (1.2)

Analysis Set definitions: PAS = Primary Analysis Set; IAS = Prior Platinum Chemotherapy;
SAS1 = Treatment-naïve; SAS2 = Prior Other Systemic Therapy; SAS3 = Non-measurable Disease.
Note: For *RET* fusion-positive NSCLC, the PAS includes the first 105 patients of the IAS. The Total column is the sum of the IAS, SAS1, SAS2, and SAS3.
1 160 mg BID is the recommended Phase 2 dose (RP2D).

Table 25. Patients Receiving Selpercatinib 160 mg BID (16 December 2019 Data cut-off):

	RET fusion-positive NSCLC					
	PAS (a subset of IAS) N = 105	IAS Prior Platinum Chemo N = 184	SAS1 Treatment - naïve N = 39	SAS2 Prior Other Systemic Therapy N = 16	SAS3 Non-measurable Disease N = 14	Total N = 253
Received at least one dose of 160 mg BID[1]	92 (87.6)	171 (92.9)	39 (100)	12 (75.0)	14 (100)	236 (93.3)
Starting dose of 160 mg BID	69 (65.7)	148 (80.4)	36 (92.3)	10 (62.5)	14 (100)	208 (82.2)
Intra-patient dose escalated to 160 mg BID	22 (21.0)	22 (12.0)	2 (5.1)	1 (6.3)	0	25 (9.9)
Dose reduced to 160 mg BID	1 (1.0)	1 (0.5)	1 (2.6)	1 (6.3)	0	3 (1.2)

Analysis Set definitions: PAS = Primary Analysis Set; IAS = Prior Platinum Chemotherapy;
SAS1 = Treatment-naïve; SAS2 = Prior Other Systemic Therapy; SAS3 = Non-measurable Disease.
Note: For *RET* fusion-positive NSCLC, the PAS includes the first 105 patients of the IAS. The Total column is the sum of the IAS, SAS1, SAS2, and SAS3.
1 160 mg BID is the recommended Phase 2 dose (RP2D).

Median time on treatment (TOT) from baseline to DCO were 10.12 months and 3.88 months for PAS and SAS1 subsets, respectively. These results were in line with the median time on study (TOS) for both subset. These observations periods, specifically the one on for the SAS1 subset are considered relatively short to establish the benefit of selpercatinib in both NSCLC settings.

Numbers analysed

The evidence supporting of the claimed indication in NSCLC came mostly from the 105 and 184 patients from the PAS and IAS respectively (2L+ NSCLC setting) and the 39 patients from SAS1 subsets (1L NSCLC setting). Sample size could be considered limited to generate evidence in the claimed indication for NSCLC.

Outcomes and estimation

Primary endpoint: ORR

Table 26. Best Overall Response, Objective Response Rate, and Clinical Benefit Rate by IRC (NSCLC Analysis Set) - Patients Enrolled by 30 March 2020

Status	PAS (N=105)	IAS (N=218)	SAS1 (N=48)	SAS2 (N=18)	SAS3 (N=18)
Best Overall Response (n, %) [1]					
Complete Response (CR)	3 (2.9)	9 (4.1)	1 (2.1)	0	1 (5.6)
Partial Response (PR)	64 (61.0)	115 (52.8)	40 (83.3)	8 (44.4)	5 (27.8)
Stable Disease (SD)	30 (28.6)	81 (37.2)	4 (8.3)	9 (50.0)	9 (50.0)
SD*	22 (21.0)	60 (27.5)	4 (8.3)	5 (27.8)	8 (44.4)
Progressive Disease (PD)	4 (3.8)	5 (2.3)	2 (4.2)	1 (5.6)	0
Not Evaluable (NE)	4 (3.8)	8 (3.7)	1 (2.1)	0	3 (16.7)
Objective Response Rate (CR + PR) [2,4]					
Number of Patients (n, %)	67 (63.8)	124 (56.9)	41 (85.4)	8 (44.4)	6 (33.3)
95% Confidence Interval	(53.9, 73.0)	(50.0, 63.6)	(72.2, 93.9)	(21.5, 69.2)	(13.3, 59.0)
Clinical Benefit Rate (CR + PR + SD*) [3,4]					
Number of Patients (n, %)	89 (84.8)	184 (84.4)	45 (93.8)	13 (72.2)	14 (77.8)
95% Confidence Interval	(76.4, 91.0)	(78.9, 89.0)	(82.8, 98.7)	(46.5, 90.3)	(52.4, 93.6)

Cutoff Date: 2020-03-30.
Percentage is calculated using the number of patients in the column heading as the denominator.
Stable Disease includes NON-CR/NON-PD.
* Indicates SD lasting >= 16 weeks following initiation of LOXO-292 until the criteria for disease progression was first met.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Objective Response Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, or PR. Response was confirmed by a repeat assessment no less than 28 days.
[3] Clinical Benefit Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or stable disease lasting 16 or more weeks (SD*). Stable disease was measured from the date of first dose of LOXO-292 until the criteria for disease progression was first met.
[4] 95% Confidence Interval was calculated using Clopper-Pearson method.

Secondary endpoints

Duration of response (DOR)

Table 27. Duration of Response by IRC with Confirmed CR or PR (NSCLC Analysis Set) - Patients Enrolled by 30 March 2020

Status	PAS (N=105)	IAS (N=218)	SAS1 (N=48)	SAS2 (N=18)	SAS3 (N=18)
Patients with Best Response of Confirmed CR or PR [1]	67	124	41	8	6
Response Status (n, %) [2]					
Disease Progression	26 (38.8)	34 (27.4)	10 (24.4)	1 (12.5)	0
Died (No Disease Progression Beforehand)	2 (3.0)	4 (3.2)	0	0	0
Censored	39 (58.2)	86 (69.4)	31 (75.6)	7 (87.5)	6 (100.0)
Reason Censored (n, %)					
Alive without Documented Disease Progression	37 (55.2)	83 (66.9)	30 (73.2)	6 (75.0)	6 (100.0)
Subsequent Anti-cancer Therapy or Cancer Related Surgery without Documented PD	2 (3.0)	3 (2.4)	1 (2.4)	1 (12.5)	0
Duration of Response (n, %)					
< 6 months	10 (14.9)	36 (29.0)	13 (31.7)	1 (12.5)	2 (33.3)
>= 6 to 12 months	21 (31.3)	51 (41.1)	17 (41.5)	4 (50.0)	3 (50.0)
>= 12 to 18 months	28 (41.8)	29 (23.4)	9 (22.0)	3 (37.5)	0
>= 18 to 24 months	5 (7.5)	5 (4.0)	2 (4.9)	0	1 (16.7)
>= 24 months	3 (4.5)	3 (2.4)	0	0	0

Duration of Response (months) [3,4]					
Median	17.51	17.51	NE	NE	NE
95% Confidence Interval for Median	12.1, NE	12.1, NE	12.0, NE	12.0, NE	NE, NE
Minimum, Maximum	3.5, 29.8+	1.8+, 29.8+	1.9+, 20.0+	3.7+, 14.8+	3.7+, 18.4+
Duration of Follow-up (months) [3]					
Median	15.67	11.99	9.79	10.43	7.39
25th, 75th Percentiles	12.1, 18.2	7.4, 15.9	7.0, 13.1	9.2, 14.4	3.7, 9.6
Rate (%) of Duration of Response [3,5]					
6 months or more	86.4	85.8	89.6	100.0	100.0
95% Confidence Interval	75.5, 92.7	77.9, 91.1	74.5, 96.0	100.0, 100.0	100.0, 100.0
12 months or more	70.3	69.1	65.0	100.0	100.0
95% Confidence Interval	57.3, 79.9	58.1, 77.8	42.8, 80.3	100.0, 100.0	100.0, 100.0

Cutoff Date: 2020-03-30.
Percentage is calculated based on the number of patients with best response of confirmed CR or PR as denominator.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Status as of the patients last disease assessment on or before cutoff date.
[3] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[4] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.
[5] 95% Confidence Interval was calculated using Greenwood's formula.

Progression free survival (PFS)

Table 28. Progression-free Survival by IRC (NSCLC Analysis Set) - Patients Enrolled by 30 March 2020

Status	PAS (N=105)	IAS (N=218)	SAS1 (N=48)	SAS2 (N=18)	SAS3 (N=18)
Status (n, %) [1]					
Disease Progression	50 (47.6)	74 (33.9)	14 (29.2)	6 (33.3)	6 (33.3)
Censored	55 (52.4)	144 (66.1)	34 (70.8)	12 (66.7)	12 (66.7)
Duration of Progression Free Survival (months) [2]					
Median	19.25	19.29	NE	NE	NE
95% Confidence Interval for Median	13.9, NE	16.5, NE	13.8, NE	3.9, NE	9.1, NE
Minimum, Maximum	0.3, 30.6+	0.0+, 30.6+	0.0+, 21.7+	1.7+, 22.0+	3.0, 19.3+
Duration of Follow-up (months)					
Median	16.76	13.60	10.84	11.53	9.23
25th, 75th Percentiles	14.7, 21.9	9.0, 16.6	9.0, 14.2	7.6, 16.1	7.2, 11.3
Rate (%) of Progression Free Survival [2,3]					
6 months or more	82.1	84.4	85.1	70.6	76.6
95% Confidence Interval	73.1, 88.3	78.7, 88.7	71.2, 92.6	43.1, 86.6	48.8, 90.5
12 months or more	65.7	69.7	67.6	70.6	53.6
95% Confidence Interval	55.5, 74.2	62.2, 75.9	49.5, 80.3	43.1, 86.6	20.9, 78.0
18 months or more	52.0	54.2	61.4	58.8	53.6
95% Confidence Interval	41.1, 61.9	44.4, 63.1	40.9, 76.6	27.5, 80.4	20.9, 78.0
24 months or more	42.0	43.7	NE	NE	NE
95% Confidence Interval	29.5, 53.9	31.5, 55.4	NE, NE	NE, NE	NE, NE

Cutoff Date: 2020-03-30.
Percentage is calculated based on the number of patients in the column heading as the denominator.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[3] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.

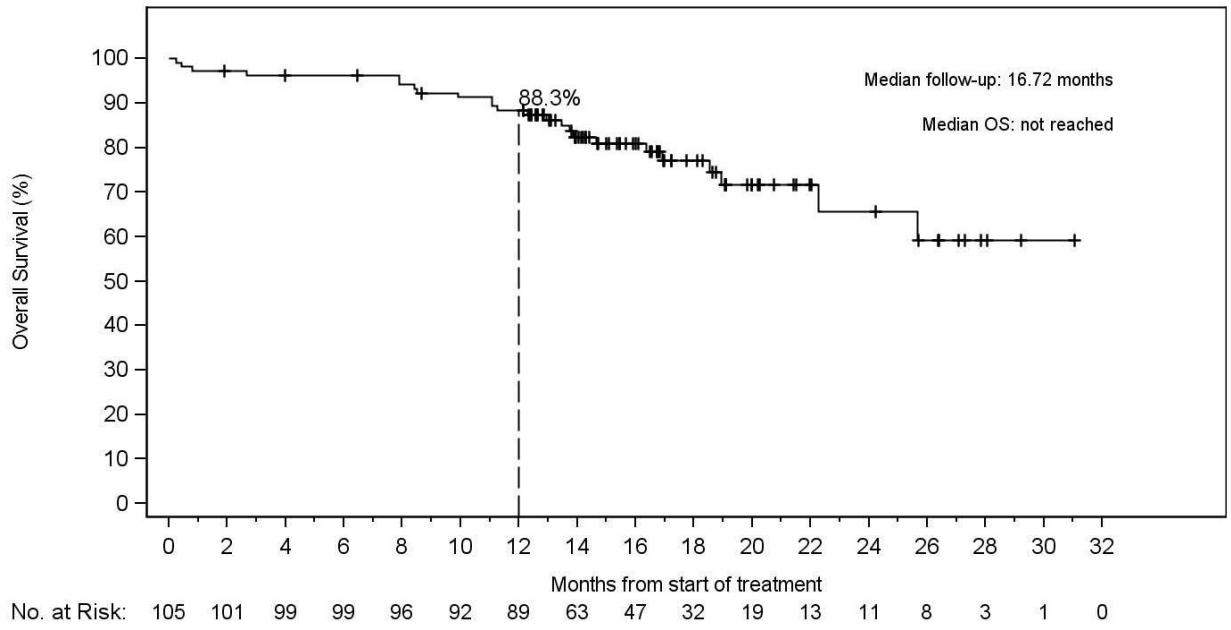
Overall survival (OS)

Median OS was not reached at the time of the DCO (23% of events observed).

Table 29. Overall Survival by IRC (NSCLC Analysis Set) - Patients Enrolled by 30 March 2020

Status	PAS (N=105)	IAS (N=218)	SAS1 (N=48)	SAS2 (N=18)	SAS3 (N=18)
Survival Status (n, %) [1]					
Disease Progression	28 (26.7)	41 (18.8)	4 (8.3)	6 (33.3)	3 (16.7)
Censored	77 (73.3)	177 (81.2)	44 (91.7)	12 (66.7)	15 (83.3)
Duration of Overall Survival (months) [2,3]					
Median	NE	NE	NE	28.88	NE
95% Confidence Interval for Median	25.7, NE	25.7, NE	NE, NE	11.0, NE	NE, NE
Minimum, Maximum	0.3, 34.5+	0.3, 34.5+	1.4, 27.2+	2.3, 28.9	3.0, 20.7+
Duration of Follow-up (months)					
Median	19.94	14.26	12.58	17.05	10.48
25th, 75th Percentiles	16.7, 23.7	10.1, 19.5	9.9, 16.7	10.3, 18.3	8.6, 12.9
Rate (%) of Overall Survival [2,3]					
6 months or more	96.2	95.4	95.8	77.0	88.9
95% Confidence Interval	90.1, 98.5	91.6, 97.5	84.4, 98.9	49.7, 90.7	62.4, 97.1
12 months or more	88.3	88.1	93.2	69.3	80.8
95% Confidence Interval	80.3, 93.2	82.5, 91.9	80.1, 97.8	40.6, 86.2	50.5, 93.6
18 months or more	78.4	77.6	88.0	69.3	80.8
95% Confidence Interval	68.8, 85.4	69.4, 83.9	68.6, 95.8	40.6, 86.2	50.5, 93.6
24 months or more	68.0	67.3	88.0	69.3	NE
95% Confidence Interval	55.3, 77.8	55.4, 76.7	68.6, 95.8	40.6, 86.2	NE, NE

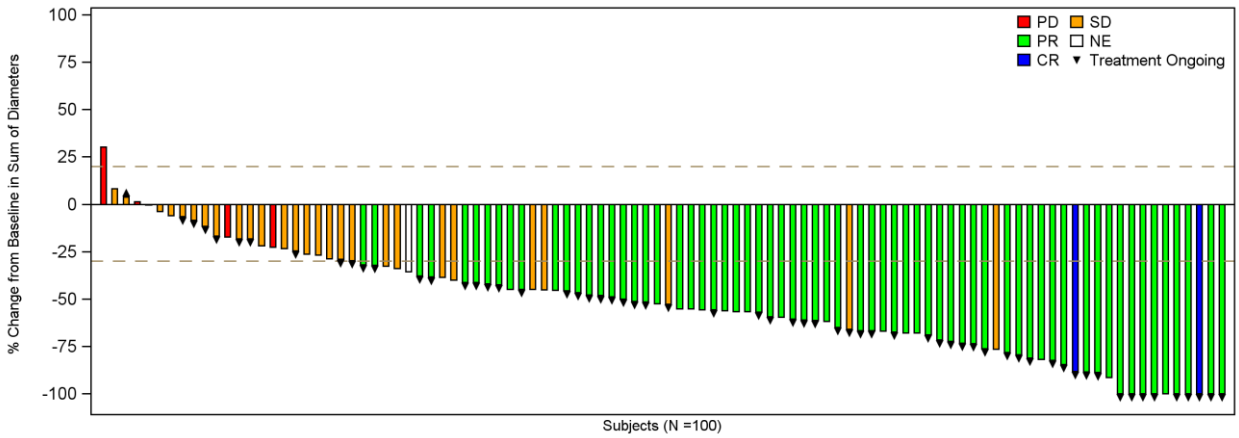
Cutoff Date: 2020-03-30.
Percentage is calculated based on the number of patients in the column heading as the denominator.
[1] Status as of the last contact on or before 30-MAR-2020.
[2] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[3] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.



Note: + = Censored.

Figure 13. Kaplan-Meier Plot of Overall Survival – Primary Analysis Set (16 December 2019 Data cut-off)

A waterfall plot illustrating the best change in tumour size per RECIST v1.1 based on IRC assessment is shown below.



Note: Five patients are not shown due to 2 patients having non-target lesions only, and 3 patients with no post-baseline target lesion measurement. (16 December 2019 Data cut-off)

Figure 14. Waterfall Plot of Best Change in Tumour Burden Based on IRC Assessment – Primary Analysis Set (16 December 2019 Data cut-off)

CNS Response in the Primary Analysis Set

Among the 253 RET fusion positive NSCLC patients (independent of analysis set), 96 had CNS metastasis and 23 had measurable CNS lesions according to IRC assessment. The ORR in the evaluable patients was 87% (20/23; 95% CI: 66.4, 97.2). The DOR was 9.36 months (range: 2.8- 23.9+).

Table 30, CNS ORR and CNS DOR – RET Fusion-positive NSCLC PAS with Measurable and Non-Measurable CNS Lesions (30 March 2020 Data cut-off)

	Measurable CNS	Non- Measurable CNS	Measurable or non-measurable CNS
N	23	73	96
CNS Best Overall Response[1], n (%)			
Complete response	5 (21.7)	25 (34.2)	30 (31.3)
Partial response	15 (65.2)	0 (0.0)	15 (15.6)
Stable disease	3 (13.0)	0 (0.0)	3 (3.1)
CNS Objective Response Rate[2,3] (CR + PR)			
n (%)	20 (87.0)	25 (34.2)	45 (46.9)
95% CI	66.4, 97.2	23.5, 46.3	36.6, 57.3
CNS Duration of Response[2, 3] (months)			
Median	9.36	NE	NE
95% CI	6.7, 12.1	NE, NE	9.3, NE
Minimum, Maximum	2.8, 23.9+	1.9+, 21.1+	1.9+, 23.9+
CNS Duration of Follow-up[2] (months)			
Median	12.98	8.71	11.99
25th, 75th Percentiles	12.0, 21.1	5.6, 12.9	7.4, 14.6
CNS Observed Duration of Response (n, %)[1]			
≥ 6 to 12 months	10 (50)	7 (28.0)	17 (37.8)
≥ 12 to 18 months	2 (10.0)	6 (24.0)	8 (17.8)
≥ 18 to 24 months	2 (10.0)	2 (8.0)	4 (8.9)

Percentage is calculated based on the number of patients with CNS best response of CR or PR as denominator.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[3] 95% confidence interval was calculated using Brookmeyer and Crowley method.

RET fusion-positive NSCLC PAS with prior anti-PD-1/PD-L1 therapy

Of the 105 RET fusion-positive NSCLC PAS patients, 58 patients also received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy (Table below). Thirteen (29%) and 17 (41%) responding patients have been in response for ≥ 12 months by IRC and investigator, respectively.

Table 31, Overview of Efficacy Results RET Fusion-Positive NSCLC Primary Analysis Set (PAS) with Prior Anti-PD-1/Anti-PD-L1 Therapy LIBRETTO-001 (16 December 2019 Data cut-off)

Status	IRC Assessment	Investigator Assessment
N	58	58
Best Overall Response, n (%)		
Complete response	1 (1.7)	1 (1.7)
Partial response	37 (63.8)	38 (65.5)
Stable disease	13 (22.4)	12 (20.7)
Progressive disease	3 (5.2)	2 (3.4)
Not evaluable	4 (6.9)	5 (8.6)
Objective Response Rate (CR + PR)		
n (%)	38 (65.5)	39 (67.2)
95% CI	(51.9, 77.5)	(53.7, 79.0)
Duration of Response (months)		
Median	NE	20.3
95% CI	12.0, NE	13.8, 21.2
Minimum, Maximum	1.9+, 26.2+	2.8, 26.0+
Duration of Response Follow-up (months)		
Median	11.9	14.8
25th, 75th Percentiles	9.2, 15.9	9.6, 21.3
Observed Duration of Response (n, %)[2]		
< 6 months	5 (13.2)	6 (15.4)
≥ 6 to 12 months	20 (52.6)	16 (41.0)
≥ 12 to 18 months	10 (26.3)	11 (28.2)
≥ 18 to 24 months	2 (5.3)	5 (12.8)
≥ 24 months	1 (2.6)	1 (2.6)
Duration of Response Status (n, %)		
Disease Progression	11 (28.9)	16 (41.0)
Died before Disease Progression	1 (2.6)	1 (2.6)
Censored	26 (68.4)	22 (56.4)

[1] Includes censored patients whose disease has not yet progressed.
NE = Not estimable; Note: + = Censored observation.

RET fusion-positive TC

Baseline data

For the primary analysis population, the median age of patients was 54 years old (range 25– 88 yo). Proportion between both sexes were well balanced (47.4% of patients were male). Most of the patients studied were White (73.7%) while 10.5% were Asian, 5.3% were Black and 5.3% were Hispanic/Latino. Median BMI value was of 25.28 suggesting a borderline overweight of the patients. ECOG performance status was reported as 0 1 (89.5%) or 2 (10.5%).

The different histologies represented in the 19 patients included: papillary (n = 13), poorly differentiated (n = 3), anaplastic (n = 2), and Hurthle cell (n = 1). The most common fusion partner was CCDC6 (47.4%) followed by NCOA4 (31.6%). Most of the patients were diagnosed by NGS on tumour. None of this population presented a concomitant Oncogenic Driver mutation.

This is considered in line with histology proportions in real life. Mostly all the patients were metastatic at diagnosis. Median time from diagnosis to study entry was of 92.30 months (range of 2.6- 401.7 months). Almost, all of the patients presented at least one measurable lesion per investigator assessment.

All of the RET-fusion positive mutant patients were previously treated at study entry; patients had received a median of 4 prior systemic therapies (range: 1 7). Prior therapies included radioactive iodine (84.2%), MKI (78.9%), other systemic therapy (42.1%).

Concerning the dose exposure to selpercatinib, 92.6% received at least one dose of 160 mg BID. Reasons why this dose was not reached for all the population are unknown.

Numbers analysed

Of the RET fusion positive thyroid cancer patients previously treated with systemic therapy other than Radioactive iodine, and enrolled in LIBRETTO-001, 22 patients had the opportunity to be followed for at least 6 months and were considered efficacy eligible. The primary assessment of efficacy was based on the first 19 of the 22 consecutively enrolled patients.

Outcomes and estimation

Table 32, Objective Response and Duration of Response – 30 March 2020 data cut-off

	Primary Analysis Set IRC Assessment
n	19
Objective Response (CR + PR)	
n (%)	78.9
95% CI	(54.4, 93.9)
Complete response n (%)	2 (10.5)
Partial response n (%)	13 (68.4)
Duration of Response (months)*	
Median	18.4
95% CI	(7.6, NE)

NE = not estimable

*Median duration of follow-up was 20.27 months (25th, 75th percentile: 12.9, 25.4) for the first 19 patients.

Table 33, Best Overall Response, Objective Response Rate, and Clinical Benefit Rate by IRC (All Treated Patients with 6-month Potential Follow Up) - RET Fusion-Positive Thyroid Analysis Set (Patients Enrolled by 30 March 2020)

Status	Treated (N=22)	Naive (N=12)	Total (N=34)
Best Overall Response (n, %) [1]			
Complete Response (CR)	2 (9.1)	4 (33.3)	6 (17.6)
Partial Response (PR)	15 (68.2)	7 (58.3)	22 (64.7)
Stable Disease (SD)	5 (22.7)	1 (8.3)	6 (17.6)
SD*	5 (22.7)	1 (8.3)	6 (17.6)
Progressive Disease (PD)	0	0	0
Not Evaluable (NE)	0	0	0
Objective Response Rate (CR + PR) [2,4]			
Number of Patients (n, %)	17 (77.3)	11 (91.7)	28 (82.4)
95% Confidence Interval	(54.6, 92.2)	(61.5, 99.8)	(65.5, 93.2)
Clinical Benefit Rate (CR + PR + SD*) [3,4]			
Number of Patients (n, %)	22 (100.0)	12 (100.0)	34 (100.0)
95% Confidence Interval	(84.6, 100.0)	(73.5, 100.0)	(89.7, 100.0)

Cutoff Date: 2020-03-30.
Percentage is calculated using the number of patients in the column heading as the denominator.
Stable Disease includes NON-CR/NON-PD.
* Indicates SD lasting >= 16 weeks following initiation of LOXO-292 until the criteria for disease progression was first met.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Objective Response Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, or PR. Response was confirmed by a repeat assessment no less than 28 days.
[3] Clinical Benefit Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or stable disease lasting 16 or more weeks (SD*). Stable disease was measured from the date of first dose of LOXO-292 until the criteria for disease progression was first met.
[4] 95% Confidence Interval was calculated using Clopper-Pearson method.

Table 34, Duration of Response by IRC with Confirmed CR or PR (All Treated Patients with 6-month Potential Follow Up) - RET Fusion-Positive Thyroid Analysis Set (Patients Enrolled by 30 March 2020)

Status	Treated (N=22)	Naive (N=12)	Total (N=34)
Patients with Best Response of Confirmed CR or PR [1]	17	11	28
Response Status (n, %) [2]			
Disease Progression	7 (41.2)	1 (9.1)	8 (28.6)
Died (No Disease Progression Beforehand)	1 (5.9)	0	1 (3.6)
Censored	9 (52.9)	10 (90.9)	19 (67.9)
Reason Censored (n, %)			
Alive without Documented Disease Progression	8 (47.1)	9 (81.8)	17 (60.7)
Subsequent Anti-cancer Therapy or Cancer Related Surgery without Documented PD	0	1 (9.1)	1 (3.6)
Discontinued from Study without Documented PD	1 (5.9)	0	1 (3.6)
Duration of Response (n, %)			
< 6 months	4 (23.5)	4 (36.4)	8 (28.6)
>= 6 to 12 months	3 (17.6)	3 (27.3)	6 (21.4)
>= 12 to 18 months	5 (29.4)	3 (27.3)	8 (28.6)
>= 18 to 24 months	3 (17.6)	1 (9.1)	4 (14.3)
>= 24 months	2 (11.8)	0	2 (7.1)
Duration of Response (months) [3,4]			
Median	18.43	NE	26.71
95% Confidence Interval for Median	10.1, NE	14.8, NE	12.8, NE
Minimum, Maximum	1.9, 26.7	3.6+, 18.5+	1.9, 26.7
Duration of Follow-up (months) [3]			
Median	20.27	9.13	12.58
25th, 75th Percentiles	12.6, 25.4	5.6, 12.2	7.7, 20.3
Rate (%) of Duration of Response [3,5]			
6 months or more	88.2	100.0	92.6
95% Confidence Interval	60.6, 96.9	100.0, 100.0	73.4, 98.1
12 months or more	74.7	100.0	82.8
95% Confidence Interval	45.5, 89.7	100.0, 100.0	59.8, 93.3

Cutoff Date: 2020-03-30.
Percentage is calculated based on the number of patients with best response of confirmed CR or PR as denominator.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Status as of the patients last disease assessment on or before cutoff date.
[3] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[4] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.
[5] 95% Confidence Interval was calculated using Greenwood's formula.

Table 35, Progression-free Survival by IRC (All Treated Patients with 6-month Potential Follow Up) - RET Fusion-Positive Thyroid Analysis Set (Patients Enrolled by 30 March 2020)

Status	Treated (N=22)	Naive (N=12)	Total (N=34)
Status (n, %) [1]			
Disease Progression	10 (45.5)	1 (8.3)	11 (32.4)
Censored	12 (54.5)	11 (91.7)	23 (67.6)
Duration of Progression Free Survival (months) [2]			
Median	20.07	NE	20.07
95% Confidence Interval for Median	10.8, NE	19.3, NE	14.5, NE
Minimum, Maximum	3.5, 30.2+	5.5+, 19.9+	3.5, 30.2+
Duration of Follow-up (months)			
Median	16.49	11.04	13.83
25th, 75th Percentiles	10.9, 27.2	7.3, 15.3	9.1, 22.0
Rate (%) of Progression Free Survival [2,3]			
6 months or more	95.5	100.0	97.1
95% Confidence Interval	71.9, 99.3	100.0, 100.0	80.9, 99.6
12 months or more	68.6	100.0	78.4
95% Confidence Interval	42.7, 84.6	100.0, 100.0	57.7, 89.8
18 months or more	52.3	100.0	65.5
95% Confidence Interval	25.2, 73.7	100.0, 100.0	40.5, 82.0
24 months or more	41.8	NE	44.9
95% Confidence Interval	15.7, 66.3	NE, NE	17.5, 69.2

Cutoff Date: 2020-03-30.
Percentage is calculated based on the number of patients in the column heading as the denominator.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[3] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.

RET mutant MTC

The disposition of patients with *RET*-mutant MTC at the 16 December 2019 Data cut-off is summarised in the table below.

Table 36, Patient Disposition (RET-mutant MTC) - 16 December 2019 Data cut-off

	PAS (a subset of IAS)	IAS Prior cabozantinib or vandetanib	SAS1 cabozantinib/ vandetanib naïve	SAS2 Non-measurable Disease	Total
Treated	55	124	88	14	226
Treatment ongoing, n (%)	37 (67.3)	92 (74.2)	81 (92.0)	13 (92.9)	186 (82.3)
Treatment discontinued, n (%)	18 (32.7)	32 (25.8)	7 (8.0)	1 (7.1)	40 (17.7)
Disease Progression	9 (16.4)	17 (13.7)	1 (1.1)	0	18 (8.0)
Adverse Event	4 (7.3)	7 (5.6)	4 (4.5)	0	11 (4.9)
Intercurrent Illness Compromising Ability to Fulfill Protocol Requirements	0	1 (0.8)	0	0	1 (0.4)
Requirement for Alternative Treatment Per Investigator	0	0	1 (1.1)	1 (7.1)	2 (0.9)
Withdrawal of Consent	1 (1.8)	2 (1.6)	1 (1.1)	0	3 (1.3)
Death	2 (3.6)	3 (2.4)	0	0	3 (1.3)
Other	2 (3.6)	2 (1.6)	0	0	2 (0.9)
Treated post-progression, n (%)	17 (30.9)	25 (20.2)	3 (3.4)	0	28 (12.4)
Study status continuing, n (%)	41 (74.5)	99 (79.8)	85 (96.6)	14 (100.0)	198 (87.6)
Study status discontinued, n (%)	14 (25.5)	25 (20.2)	3 (3.4)	0	28 (12.4)
Withdrawal of consent	3 (5.5)	6 (4.8)	1 (1.1)	0	7 (3.1)
Lost to follow-up	1 (1.8)	1 (0.8)	0	0	1 (0.4)
Death	10 (18.2)	18 (14.5)	2 (2.3)	0	20 (8.8)

Note: For *RET*-mutant MTC, the PAS includes the first 55 patients of the IAS. The Total column is the sum of the IAS, SAS1, and SAS2.

Baseline data

The baseline demographic characteristics of patients with RET-mutant MTC at the 16 December 2019 Data cut-off are summarised in the table below.

Table 37. Summary - Demographics - 16 December 2019 Data cut-off

	***RET*-mutant MTC**				
	PAS (a subset of IAS) N = 55	**IAS Prior cabozantinib or vandetanib N = 124**	**SAS1 cabozantinib/ vandetanib-naïve N = 88**	**SAS2 Non-measurable Disease N = 14**	**Total N = 226**

Age, years					
Median	57.0	57.5	58.0	60.5	58
Range	17-84	17-90	15-82	30-74	15-90
Overall age group, n (%)					
<18 years	1 (1.8)	1 (0.8)	2 (2.3)	0	3 (1.3)
18–44 years	9 (16.4)	21 (16.9)	20 (22.7)	5 (35.7)	46 (20.4)
45–64 years	27 (49.1)	59 (47.6)	43 (48.9)	6 (42.9)	108 (47.8)
65–74 years	12 (21.8)	32 (25.8)	14 (15.9)	3 (21.4)	49 (21.7)
≥ 75 years	6 (10.9)	11 (8.9)	9 (10.2)	0	20 (8.8)
Sex, n (%)					
Male	36 (65.5)	81 (65.3)	58 (65.9)	9 (64.3)	148 (65.5)
Female	19 (34.5)	43 (34.7)	30 (34.1)	5 (35.7)	78 (34.5)
Race, n (%)					
White	49 (89.1)	111 (89.5)	76 (86.4)	13 (92.9)	200 (88.5)
Black	1 (1.8)	2 (1.6)	0	0	2 (0.9)
Asian	0	1 (0.8)	4 (4.5)	1 (7.1)	6 (2.7)
Other/Missing	5 (9.1)	10 (8.1)	8 (9.1)	0	18 (8.0)
Range	150-196	150-196	150-199	159-203	150-203
Body mass index, kg/m^2					
n	55	119	83	14	216
Median	24.24	22.99	24.85	24.93	23.52
Range	16.4-59.1	15.2-59.1	11.6-49.6	17.9-35.3	11.6-59.1
Baseline ECOG, n (%)					
0	11 (20.0)	31 (25.0)	43 (48.9)	8 (57.1)	82 (36.3)
1	41 (74.5)	84 (67.7)	42 (47.7)	6 (42.9)	132 (58.4)
2	3 (5.5)	9 (7.3)	3 (3.4)	0	12 (5.3)

Analysis set definitions: PAS = Primary Analysis Set; IAS = Prior Cabozantinib or Vandetanib; SAS1 = Cabozantinib/vandetanib-naïve; SAS2 = Non-measurable Disease.
Note: For *RET*- mutant MTC, the PAS includes the first 55 patients from IAS. The "Total" column is the sum of the IAS, SAS1, and SAS2.

The baseline disease characteristics of patients with RET-mutant MTC at the 16 December 2019 Data cut-off are summarised in the table below.

Table 38. Summary- Baseline Disease Characteristics - 16 December 2019 Data cut-off

	***RET*-mutant MTC**				
Characteristic	**PAS (a subset of IAS) N = 55**	**IAS Prior cabozantinib or vandetanib N = 124**	**SAS1 cabozantinib / vandetanib-naïve N = 88**	**SAS2 Non-measurable Disease N = 14**	**Total N = 226**
Primary Tumour Type, n (%)					
Medullary Thyroid Cancer	55 (100.0)	124 (100.0)	88 (100.0)	14 (100.0)	226 (100.0)
Stage at Initial Diagnosis, n (%)					
I	0	1 (0.8)	0	0	1 (0.4)
II	0	0	2 (2.3)	0	2 (0.9)
IIB	0	0	1 (1.1)	0	1 (0.4)
III	1 (1.8)	2 (1.6)	0	0	2 (0.9)
IIIA	1 (1.8)	1 (0.8)	0	0	1 (0.4)
IV	33 (60.0)	66 (53.2)	42 (47.7)	6 (42.9)	114 (50.4)
IVA	6 (10.9)	11 (8.9)	7 (8.0)	2 (14.3)	20 (8.8)
IVB	0	2 (1.6)	2 (2.3)	1 (7.1)	5 (2.2)

IVC	12 (21.8)	38 (30.6)	31 (35.2)	5 (35.7)	74 (32.7)
Missing	2 (3.6)	3 (2.4)	3 (3.4)	0	6 (2.7)
Time from Diagnosis, Months					
Median	65.3	61.9	56.40	56.10	59.80
Range	3.3-417.9	3.3-454.6	1.4-522.8	5.3-428.7	1.4-522.8
History of Metastatic Disease, n (%)					
Yes	54 (98.2)	122 (98.4)	88 (100.0)	13 (92.9)	223 (98.7)
No	1 (1.8)	2 (1.6)	0	1 (7.1)	3 (1.3)
Time from Diagnosis of Metastatic Disease, Months					
Median	43.35	51.70	44.55	35.20	48.10
Range	3.3-299.9	0.5-299.9	0.5-522.8	6.9-321.1	0.5-522.8
Presence of Diarrhoea at Baseline, n (%)					
Yes	33 (60.0)	77 (62.1)	54 (61.4)	7 (50.0)	138 (61.1)
No	22 (40.0)	47 (37.9)	34 (38.6)	7 (50.0)	88 (38.9)
Calcitonin (pg/ml)					
n	54	123	88	14	225
Median	6364.5	4969.0	4956.5	3821.2	4761.0
Range	66-169521	1-200000	51-151354	185-82106	1-200000
CEA (ng/ml)					
n	55	124	87	14	225
Median	151.90	133.55	61.80	31.45	93.00
Range	2.3-12412.0	1.7-12412.0	1.0-14515.0	3.5-551.2	1.0-14515.0
Tumour Burden (At least one measurable lesion per Investigator), n (%)					
Yes	53 (96.4)	122 (98.4)	86 (97.7)	0	208 (92.0)
No	2 (3.6)	2 (1.6)	2 (2.3)	14 (100.0)	18 (8.0)

Analysis set definitions: PAS = Primary Analysis Set; IAS = Prior Cabozantinib or Vandetanib; SAS1 = Cabozantinib/vandetanib-naïve; SAS2 = Non-measurable Disease.
Note: For *RET*- mutant MTC, the PAS includes the first 55 patients from IAS. The "Total" column is the sum of the IAS, SAS1, and SAS2.

The most common mutation was M918T (60%), followed by extracellular cysteine mutations (12.7%). The majority of the patients were diagnosed by NGS on tumour. None of the MTC mutated patients presented a concomitant oncogenic driver mutation.

The summary of previous therapies patients with RET-mutant MTC at the 16 December 2019 Data cut-off are summarised in the table below.

Table 39. Summary- Prior Cancer-Related Treatments - 16 December 2019 Data cut-off

	***RET*-mutant MTC**				
Characteristic	**PAS (a subset of IAS) N = 55**	**IAS Prior cabozantinib or vandetanib N = 124**	**SAS1 cabozantinib/ vandetanib-naïve N = 88**	**SAS2 Non-measurable Disease N = 14**	**Total N = 226**
Received prior systemic therapy, n (%)					
Yes	55 (100.0)	124 (100.0)	16 (8.2)	8 (57.1)	148 (65.5)
No	0	0	72 (81.8)	6 (42.9)	78 (34.5)
Type of Prior Systemic Therapy, n (%)					
MKI	55 (100.0)	124 (100.0)	7 (8.0)	7 (50.0)	138 (61.1)
Chemotherapy	7 (12.7)	15 (12.1)	3 (3.4)	0	18 (8.0)
Radioactive Iodine	0	0	1 (1.1)	1 (7.1)	2 (0.9)
Anti-PD1/PD-L1 Therapy	8 (14.5)	11 (8.9)	2 (2.3)	0	13 (5.8)
Taxane Chemotherapy	1 (1.8)	3 (2.4)	1 (1.1)	0	4 (1.8)
Other Systemic Therapy	8 (14.5)	18 (14.5)	6 (6.8)	0	24 (10.6)
Prior systemic therapy, n (%)					
0	0	0	72 (81.8)	6 (42.9)	78 (34.5)
1–2	37 (67.3)	88 (71.0)	16 (18.2)	7 (50.0)	111 (49.1)
≥ 3	18 (32.7)	36 (29.0)	0	1 (7.1)	37 (16.4)

Prior Systemic Regimens					
Median	2.0	2.0	0.0	1.0	1.0
Range	1-8	1-8	0-2	0-5	0-8
Best Response to Last Systemic Treatment, n (%)					
Partial response	4 (7.3)	14 (11.3)	4 (4.5)	1 (7.1)	19 (8.4)
Stable disease	17 (30.9)	48 (38.7)	3 (3.4)	4 (28.6)	55 (24.3)
Progressive disease	19 (34.5)	32 (25.8)	6 (6.8)	0	38 (16.8)
Not Evaluable	15 (27.3)	30 (24.2)	3 (3.4)	3 (21.4)	36 (15.9)
Unknown	0	0	72 (81.8)	6 (42.9)	78 (34.5)
Prior Radiotherapy, n (%)	33 (60.0)	67 (54.0)	30 (34.1)	7 (50.0)	104 (46.0)
Prior Cancer-related Surgery, n (%)	50 (90.9)	111 (89.5)	73 (83.0)	12 (85.7)	196 (86.7)

Analysis set definitions: PAS = Primary Analysis Set; IAS = Prior Cabozantinib or Vandetanib treatment; SAS1 = Cabozantinib/Vandetanib-naïve; SAS2 = Non-measurable Disease.
Note: For *RET*- mutant MTC, the PAS includes the first 55 patients from IAS. The "Total" column is the sum of the IAS, SAS1, and SAS2.

Related to the exposure to Selpercatinib, not all the patients had received at least one dose of 160 mg BID. Median time on treatment was 11.86 months in the PAS population whereas it was 7.28 months, 5.47 and 5.45 months for the IAS, SAS1 and SAS2 subpopulations, respectively. Median values for time of study were mostly in line with those for time on treatment. This exposure is considered relatively low and the follow-up time not enough to evidence the efficacy profile of the selpercatinib in the intended indication.

Table 40. A Selpercatinib Starting Doses- 16 December 2019 Data cut-off

	***RET*-mutant MTC**				
	PAS (a subset of IAS) N = 55	**IAS Prior cabozantinib or vandetanib N = 124**	**SAS1 cabozantinib /vandetanib naïve N = 88**	**SAS2 Non measurable Disease N = 14**	**Total N = 226**
Starting Dose, n (%)					
20 mg QD	1 (1.8)	1 (0.8)	0	0	1 (0.4)
20 mg BID	3 (5.5)	3 (2.4)	0	0	3 (1.3)
40 mg BID	4 (7.3)	4 (3.2)	1 (1.1)	0	5 (2.2)
60 mg BID	2 (3.6)	2 (1.6)	1 (1.1)	0	3 (1.3)
80 mg BID	8 (14.5)	8 (6.5)	3 (3.4)	0	11 (4.9)
120 mg BID	2 (3.6)	2 (1.6)	1 (1.1)	0	3 (1.3)
160 mg BID	31 (56.4)	100 (80.6)	81 (92.0)	14 (100.0)	195 (86.3)
200 mg BID	3 (5.5)	3 (2.4)	0	0	3 (1.3)
240 mg BID	1 (1.8)	1 (0.8)	1 (1.1)	0	2 (0.9)

Note: For *RET*-mutant MTC, the PAS includes the first 55 patients from IAS. The "Total" column is the sum of the IAS, SAS1, and SAS2.

Table 41. Patients who received at least One Dose of 160mg BID Selpercatinib- 16 December 2019 Data cut-off

Status	***RET*-mutant MTC**				
	PAS (a subset of IAS) N = 55	**IAS Prior cabozantinib or vandetanib N = 124**	**SAS1 cabozantinib /vandetanib naïve N = 88**	**SAS2 Nonmeasurable Disease N = 14**	**Total N = 226**

Received at least one dose of 160 mg BID	45 (81.8)	114 (91.9)	86 (97.7)	14 (100.0)	214 (94.7)
Starting dose of 160 mg BID[1]	31 (56.4)	100 (80.6)	81 (92.0)	14 (100.0)	195 (86.3)
Intra-patient dose escalated to 160 mg BID	13 (23.6)	13 (10.5)	5 (5.7)	0	18 (8.0)
Dose reduced to 160 mg BID	1 (1.8)	1 (0.8)	0	0	1 (0.4)

Note: For *RET*-mutant MTC, the PAS includes the first 55 patients from IAS. The "Total" column is the sum of the IAS, SAS1, and SAS2.

[1] 160 mg BID is the recommended Phase 2 dose (RP2D).

Table 42. Time on Treatment - 16 December 2019 Data cut-off

Status	***RET*-mutant MTC**				
	PAS (a subset of IAS) N = 55	**IAS Prior cabozantinib or vandetanib N = 124**	**SAS1 cabozantinib/ vandetanibnaïve N = 88**	**SAS2 Nonmeasurable Disease N = 14**	**Total N = 226**
Time on Treatment (TOT), Months					
Median	17.18	12.02	11.45	11.43	11.84
Range	0.4-29.9	0.2-29.9	0.2-26.4	7.9-16.5	0.2-29.9

Note: For RET-mutant MTC, the PAS includes the first 55 patients from IAS. The "Total" column is the sum of the IAS, SAS1, and SAS2.

Table 43. Time on Study- 16 December 2019 Data cut-off

Status	***RET*-mutant MTC**				
	PAS (a subset of IAS) N = 55	**IAS Prior cabozantinib or vandetanib N = 124**	**SAS1 cabozantinib /vandetanib naïve N = 88**	**SAS2 Nonmeasurable Disease N = 14**	**Total N = 226**
Time On Study (TOS), months					
Median	17.71	12.68	11.99	11.43	12.16
Range	1.1-29.9	0.4-29.9	2.2-26.4	7.9-16.5	0.4-29.9

Note: For RET-mutant MTC, the PAS is the first 55 patients of the IAS. The "Total" column is the sum of the IAS, SAS1, and SAS2.

Numbers analysed

For RET-mutant MTC, the analysis sets include a PAS, IAS and 2 supplemental analysis sets (SAS1 & SAS2). The PAS and SAS1 primarily support the indication for *advanced RET-mutant MTC in patients who require systemic therapy*.

Outcomes and estimation

Primary endpoint: ORR

Table 44. Best Overall Response, Objective Response Rate, and Clinical Benefit Rate by IRC (All Treated Patients with 6-month Potential Follow Up) - MTC Analysis Set (Patients Enrolled by 30 March 2020)

Status	PAS (N=55)	IAS (N=143)	SAS1 (N=112)	SAS1 pre-treated (N=22)	SAS1 naïve (N=90)	SAS2 (N=19)
Best Overall Response (n, %) [1]						
Complete Response (CR)	6 (10.9)	6 (4.2)	10 (8.9)	1 (4.5)	9 (10.0)	3 (15.8)
Partial Response (PR)	32 (58.2)	93 (65.0)	70 (62.5)	10 (45.5)	60 (66.7)	2 (10.5)
Stable Disease (SD)	14 (25.5)	35 (24.5)	28 (25.0)	11 (50.0)	17 (18.9)	12 (63.2)
SD*	13 (23.6)	31 (21.7)	25 (22.3)	10 (45.5)	15 (16.7)	12 (63.2)
Progressive Disease (PD)	1 (1.8)	2 (1.4)	2 (1.8)	0	2 (2.2)	0
Not Evaluable (NE)	2 (3.6)	7 (4.9)	2 (1.8)	0	2 (2.2)	2 (10.5)
Objective Response Rate (CR + PR) [2,4]						
Number of Patients (n, %)	38 (69.1)	99 (69.2)	80 (71.4)	11 (50.0)	69 (76.7)	5 (26.3)
95% Confidence Interval	(55.2, 80.9)	(61.0, 76.7)	(62.1, 79.6)	(28.2, 71.8)	(66.6, 84.9)	(9.1, 51.2)
Clinical Benefit Rate (CR + PR + SD*) [3,4]						
Number of Patients (n, %)	51 (92.7)	130 (90.9)	105 (93.8)	21 (95.5)	84 (93.3)	17 (89.5)
95% Confidence Interval	(82.4, 98.0)	(85.0, 95.1)	(87.5, 97.5)	(77.2, 99.9)	(86.1, 97.5)	(66.9, 98.7)

Cutoff Date: 2020-03-30.
Percentage is calculated using the number of patients in the column heading as the denominator.
Stable Disease includes NON-CR/NON-PD.
* Indicates SD lasting >= 16 weeks following initiation of LOXO-292 until the criteria for disease progression was first met.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Objective Response Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, or PR. Response was confirmed by a repeat assessment no less than 28 days.
[3] Clinical Benefit Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or stable disease lasting 16 or more weeks (SD*). Stable disease was measured from the date of first dose of LOXO-292 until the criteria for disease progression was first met.
[4] 95% Confidence Interval was calculated using Clopper-Pearson method.

Secondary endpoints

Duration of response (DOR)

Table 45. Duration of Response by IRC with Confirmed CR or PR (All Treated Patients with 6-month Potential Follow Up) MTC Analysis Set - Patients Enrolled by 30 March 2020

Status	PAS (N=55)	IAS (N=143)	SAS1 (N=112)	SAS1 pre-treated (N=22)	SAS1 naïve (N=90)	SAS2 (N=19)
Patients with Best Response of Confirmed CR or PR [1]	38	99	80	11	69	5
Response Status (n, %) [2]						
Disease Progression	8 (21.1)	17 (17.2)	4 (5.0)	0	4 (5.8)	0
Died (No Disease Progression Beforehand)	1 (2.6)	1 (1.0)	1 (1.3)	0	1 (1.4)	0
Censored	29 (76.3)	81 (81.8)	75 (93.8)	11 (100.0)	64 (92.8)	5 (100.0)
Reason Censored (n, %)						
Alive without Documented Disease Progression	26 (68.4)	75 (75.8)	74 (92.5)	11 (100.0)	63 (91.3)	5 (100.0)
Subsequent Anti-cancer Therapy or Cancer Related Surgery without Documented PD	2 (5.3)	5 (5.1)	0	0	0	0
Discontinued from Study without Documented PD	1 (2.6)	1 (1.0)	1 (1.3)	0	1 (1.4)	0
Duration of Response (n, %)						
< 6 months	6 (15.8)	32 (32.3)	30 (37.5)	2 (18.2)	28 (40.6)	2 (40.0)
>= 6 to 12 months	6 (15.8)	31 (31.3)	25 (31.3)	3 (27.3)	22 (31.9)	3 (60.0)
>= 12 to 18 months	14 (36.8)	24 (24.2)	17 (21.3)	4 (36.4)	13 (18.8)	0
>= 18 to 24 months	8 (21.1)	8 (8.1)	7 (8.8)	2 (18.2)	5 (7.2)	0
>= 24 months	4 (10.5)	4 (4.0)	1 (1.3)	0	1 (1.4)	0
Duration of Response (months) [3,4]						
Median	NE	NE	21.95	NE	21.95	NE
95% Confidence Interval for Median	19.1,NE	19.1,NE	21.9,NE	NE,NE	21.9,NE	NE,NE
Minimum, Maximum	2.8+,26.7+	1.7+,26.7+	1.5+,24.1+	1.8+,20.4+	1.5+,24.1+	3.5+,10.3+
Duration of Follow-up (months) [3]						
Median	17.45	10.05	9.26	13.86	9.23	9.23
25th, 75th Percentiles	12.9, 22.0	5.9, 15.9	5.6, 14.7	7.5, 17.9	5.6, 14.6	3.7, 9.3
Rate (%) of Duration of Response [3,5]						
6 months or more	94.5	90.7	96.2	100.0	95.4	100.0
95% Confidence Interval	79.8, 98.6	82.2, 95.2	85.6, 99.0	100.0,100.0	82.8, 98.8	100.0,100.0
12 months or more	85.2	79.8	91.5	100.0	89.7	NE
95% Confidence Interval	68.0, 93.6	67.5, 87.8	78.7, 96.8	100.0,100.0	74.4, 96.1	NE,NE

Cutoff Date: 2020-03-30.
Percentage is calculated based on the number of patients with best response of confirmed CR or PR as denominator.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Status as of the patients last disease assessment on or before cutoff date.
[3] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[4] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.
[5] 95% Confidence Interval was calculated using Greenwood's formula.

Progression free survival (PFS)

Table 46. PFS by IRC (All Treated Patients with 6-month Potential Follow Up) MTC Analysis Set - Patients Enrolled by 30 March 2020

Status	PAS (N=55)	IAS (N=143)	SAS1 (N=112)	SAS1 Pre-treated (N=22)	SAS1 Naive (N=90)	SAS2 (N=19)
Status (n, %) [1]						
Disease Progression	16 (29.1)	36 (25.2)	9 (8.0)	1 (4.5)	8 (8.9)	1 (5.3)
Censored	39 (70.9)	107 (74.8)	103 (92.0)	21 (95.5)	82 (91.1)	18 (94.7)
Duration of Progression Free Survival (months) [2]						
Median	NE	NE	NE	NE	NE	NE
95% Confidence Interval for Median	24.4, NE	20.0, NE	23.6, NE	NE, NE	23.6, NE	NE, NE
Minimum, Maximum	0.0+, 32.2+	0.0+, 32.2+	0.0+, 25.8+	1.7+, 22.2+	0.0+, 25.8+	5.0+, 19.1+
Duration of Follow-up (months)						
Median	20.27	13.90	11.10	13.73	11.10	11.73
25th, 75th Percentiles	19.1, 27.6	9.3, 19.3	7.6, 16.6	9.1, 19.4	7.6, 16.5	7.4, 14.1
Rate (%) of Progression Free Survival [2,3]						
6 months or more	92.4	89.5	98.2	100.0	97.7	94.1
95% Confidence Interval	81.0, 97.1	82.9, 93.7	92.9, 99.5	100.0, 100.0	91.2, 99.4	65.0, 99.1
12 months or more	82.3	76.9	92.9	100.0	91.0	94.1
95% Confidence Interval	68.7, 90.4	67.9, 83.7	84.5, 96.8	100.0, 100.0	80.8, 95.9	65.0, 99.1
18 months or more	73.8	67.9	88.7	91.7	88.3	94.1
95% Confidence Interval	59.1, 83.9	57.0, 76.6	78.0, 94.4	53.9, 98.8	76.1, 94.5	65.0, 99.1
24 months or more	66.8	61.4	59.2	NE	58.8	NE
95% Confidence Interval	50.1, 79.0	48.0, 72.4	8.8, 89.3	NE, NE	8.8, 89.1	NE, NE

Cutoff Date: 2020-03-30.
Percentage is calculated based on the number of patients in the column heading as the denominator.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[3] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.

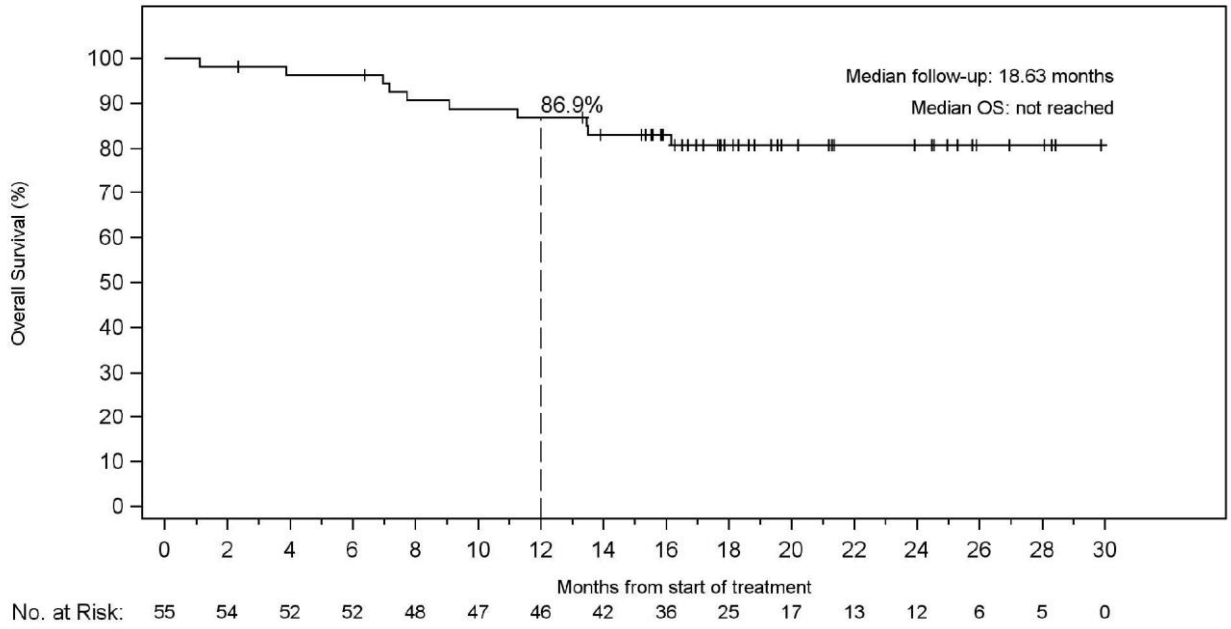
Overall survival (OS)

Table 47. OS by IRC (All Treated Patients with 6-month Potential Follow Up) MTC Analysis Set - Patients Enrolled by 30 March 2020

Status	PAS (N=55)	IAS (N=143)	SAS1 (N=112)	SAS1 Pre-treated (N=22)	SAS1 Naive (N=90)	SAS2 (N=19)
Survival Status (n, %) [1]						
Disease Progression	13 (23.6)	26 (18.2)	2 (1.8)	0 (0.0)	2 (2.2)	0 (0.0)
Censored	42 (76.4)	117 (81.8)	110 (98.2)	22 (100.0)	88 (97.8)	19 (100.0)
Duration of Overall Survival (months) [2,3]						
Median	33.25	33.25	NE	NE	NE	NE
95% Confidence Interval for Median	33.2, NE	33.2, NE	23.6, NE	NE, NE	23.6, NE	NE, NE
Minimum, Maximum	1.1, 33.3+	0.4+, 33.3+	2.2+, 29.8+	6.1+, 22.8+	2.2+, 29.8+	6.8+, 19.9+
Duration of Follow-up (months)						
Median	22.08	15.70	13.83	15.56	13.60	14.19
25th, 75th Percentiles	19.9, 28.3	11.3, 21.1	9.6, 18.4	9.1, 20.0	9.7, 17.4	9.4, 17.4
Rate (%) of Overall Survival [2,3]						
6 months or more	96.3	94.3	100.0	100.0	100.0	100.0
95% Confidence Interval	86.1, 99.1	88.9, 97.1	100.0, 100.0	100.0, 100.0	100.0, 100.0	100.0, 100.0
12 months or more	86.9	86.9	100.0	100.0	100.0	100.0
95% Confidence Interval	74.4, 93.5	79.7, 91.6	100.0, 100.0	100.0, 100.0	100.0, 100.0	100.0, 100.0
18 months or more	77.1	76.7	98.5	100.0	98.1	100.0
95% Confidence Interval	63.2, 86.3	66.8, 84.0	89.9, 99.8	100.0, 100.0	87.4, 99.7	100.0, 100.0
24 months or more	77.1	76.7	82.1	NE	81.8	NE
95% Confidence Interval	63.2, 86.3	66.8, 84.0	29.6, 96.9	NE, NE	30.1, 96.7	NE, NE

Cutoff Date: 2020-03-30.
Percentage is calculated based on the number of patients in the column heading as the denominator.
[1] Status as of the last contact on or before 30-MAR-2020.
[2] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[3] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.

The Kaplan-Meier curve for the Primary analysis set at the 16 December 2019 data cut-off is included below.



Note: + = Censored.

Figure 15. Kaplan-Meier Plot of Overall Survival – Primary Analysis Set - 16 December 2019 Data cut-off

Ancillary analyses

Analysis by subgroups in the PAS MTC population did not revealed any remarkable difference to main analysis. Overall, ORR were mostly in line with the main analysis.

- **ORR and DoR – Special populations**

Table 48. ORR and DOR by Demographics Based on IRC Assessment – Primary Analysis Set (16 December 2019 Data cut-off)

	N	Responders	ORR% (95% CI)	DOR mon (Range)
Overall	55	38	69.1% (55.2, 80.9)	NE (2.8+, 24.0+)
Age				
< 65 years	37	25	67.6% (50.21, 81.99)	NR (2.76+, 23.95+)
≥ 65 years	18	13	72.2% (46.52, 90.31)	NR (3.48+, 17.48+)
Sex				
Male	36	25	69.4% (51.89, 83.65)	NR (2.76+, 23.95+)
Female	19	13	68.4% (43.45, 87.42)	19.12 (2.79+, 19.12)
Race				
White	49	34	69.4% (54.58, 81.75)	NR (2.76+, 23.95+)
Other	6	4	66.7% (22.28, 95.67)	NR (2.79+, 22.87+)
ECOG				
0	11	8	72.7% (39.03, 93.98)	19.12 (4.24, 22.14+)
1-2	44	30	68.2% (52.42, 81.39)	NR (2.76+, 23.95+)
Any Metastatic Disease				
Yes	54	37	68.5% (54.45, 80.48)	NR (2.76+, 23.95+)
No	1	1	PR (NA)	NR (16.10+)

NA = Not applicable; NE = Not estimable; NR = Not reached; Note: + = Censored observation.

Table 49. ORR and DOR by RET Mutation Type and Type of Molecular Assay based on IRC Assessment – Primary Analysis Set (16 December 2019 Data cut-off)

	N	Responders	ORR% (95% CI)	DOR mon (Range)
Overall	55	38	69.1% (55.2, 80.9)	NE (2.8+, 24.0+)
***RET* Mutation Type**				
M918T	33	21	63.6% (45.12, 79.60)	19.12 (2.79+, 23.13+)
Extracellular Cysteine Mutation	7	5	71.4% (29.04, 96.33)	NR (2.76+, 18.14+)
V804M/L[1]	5	3	60.0% (14.66, 94.73)	NR (14.75+, 22.87+)
Other	10	9	90.0% (55.50, 99.75)	NR (3.48+, 23.95+)
Type of *RET* Molecular Assay				
NGS on Blood or Plasma	2	1	PR, SD	NR (2.83+)
NGS on Tumour	43	31	72.1% (56.33, 84.67)	NR (2.76+, 23.95+)
PCR	9	5	55.6% (21.20, 86.30)	NR (9.17+, 22.87+)

Other	1	1	PR	5.55 (5.55)

NE = Not estimable; NR = Not reached; Note: + = Censored patients.
1 Patient has either V804M or V804L mutation.

Table 50. ORR and DOR by Number and Type of Prior Therapy Based on IRC Assessment – Primary Analysis Set (16 December 2019 Data cut-off)

Baseline Characteristic	N	CR + PR	ORR % (95% CI)	DOR mon (Range)
Overall	55	38	69.1% (55.2, 80.9)	NE (2.8+, 24.0+)
Number of prior therapies				
1–2	37	24	64.9% (47.46, 79.79)	NR (2.76+, 23.95+)
3 or more	18	14	77.8 % (52.36, 93.59)	NR (2.79+, 23.13+)
Type of Prior Systemic Therapy				
Prior cabozantinib only	13	9	69.2% (38.57, 90.91)	NR (2.79+, 16.59+)
Prior vandetanib only	18	12	66.7% (40.99, 86.66)	NR (2.76+, 23.95+)
Prior cabozantinib and vandetanib	24	17	70.8% (48.91, 87.38)	NR (2.79+, 23.13+)

NE = Not estimable; NR = Not reached; Note: + = Censored observation.

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 51. Summary of efficacy for trial LIBRETTO-001

Title: A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer and Other Tumors with RET Activation (LIBRETTO-001)		
Study identifier	LOXO-RET-17001; LIBRETTO-001	
Design	Phase 1/2, multicentre, open-label	
	Duration of main phase:	The study is ongoing.
	Duration of Run-in phase:	Not provided
	Duration of Extension phase	The study is ongoing.

Hypothesis	*For the RET-Fusion Positive NSCLC Primary Analysis Set:* • A true ORR of ≥ 50% is hypothesized when selpercatinib is administered to patients with *RET* fusion-positive NSCLC who progressed on or after receipt of platinum-based chemotherapy. • A sample size of 105 patients is estimated to provide more than 98% power to achieve a lower boundary of a 2-sided 95% exact binomial confidence interval (CI) about the estimated ORR that exceeds 30%. *For the RET-Mutant MTC Primary Analysis Set:* • A true ORR of ≥ 40% is hypothesized when selpercatinib 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%.			
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, version 1.1.	
	Secondary endpoint	duration of response (DOR) by IRC	Number of months from the start date of PR or CR (whichever response is recorded first), and subsequently confirmed, to the date of disease progression or death, whichever occurs earlier.	
	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 (whatever the cause).	
	Secondary endpoint	Overall survival (OS)	The number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause). Patients who are alive or lost to follow-up as of the data cutoff date will be right-censored. The censoring date will be determined from the date the patient was last known to be alive.	
Database lock	09 August 2019			
Results and Analysis				
Analysis description	***RET-Fusion Positive NSCLC (Prior Platinum Chemotherapy for PAS and IAS and treatment naïve patients for SAS1)*** *Data cut-off date: 30 March 2020*			
Analysis population and time point description	Analysis set	PAS	IAS	SAS1
Descriptive statistics and estimate variability	Number of patients	105	218	48
	Primary analysis: ORR % (95% CI) by IRC	63.8 (53.9, 73.0)	56.9 (50.0, 63.6)	85.4 (72.2, 93.9)
	DOR median, months (95% CI) by IRC	17.51 (12.1, NE)	17.51 (12.1, NE)	NE (12.0, NE)

	PFS median, months (95% CI) by IRC	19.25 (13.9, NE)	19.29 (16.5, NE)	NE (13.8, NE)
	OS median, months (95% CI) by IRC	NE (25.7, NE)	NE (25.7, NE)	NE (NE, NE)
Analysis population and time point description	***RET-Mutant MTC (Prior Cabozantinib or Vandetanib Treatment for PAS and IAS and treatment naïve patients for SAS1)*** *Data cut-off date: 30 March 2020*			
	Analysis set	PAS	IAS	SAS1
Descriptive statistics and estimate variability	Number of patients	55	143	90
	ORR % (95% CI) by IRC	69.1 (55.2, 80.9)	69.2 (61.0, 76.7)	76.7 (66.6, 84.9)
	DOR median, months (95% CI) by IRC	NE (19.1, NE)	NE (19.1, NE)	21.95 (21.9, NE)
	PFS median, months (95% CI) by IRC	NE (24.4, NE)	NE (20.0, NE)	NE (23.6, NE)
	OS median, months (95% CI) by IRC	33.25 (33.2 , NE)	33.25 (33.2, NE)	NE (23.6, NE)
Analysis population and time point description	***RET fusion-positive Thyroid Cancer previously treated with systemic therapy*** *Data cut-off date: 30 March 2020*			
	Analysis set		PAS	Efficacy eligible patients
Descriptive statistics and estimate variability	Number of patients		19	22
	ORR % (95% CI) by IRC		78.9 (54.4, 93.9)	77.3 (54.6, 92.2)
	DOR median, months (95% CI) by IRC		18.4 (7.6, NE)	18.4 (10.1, NE)
	PFS median, months (95% CI) by IRC		20.07 (9.4, NE)	20.07 (10.8, NE)

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

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)**
Non Controlled Trials	183	61	8

2.5.3. Discussion on clinical efficacy

The main evidence supporting this CMA request is coming from a pivotal phase I/II study to determine the MTD/RP2D and to assess the efficacy and safety of selpercatinib in patients with RET-fusion positive solid tumours, RET-mutant MTC and other tumours with RET activation (study LiBRETTO-001/ LOXO-RET-17001).

The applicant has decided not to pursue the use of selpercatinib in treatment naïve patients with *RET* fusion-positive NSCLC or cabozantinib and vandetanib treatment naive patients with *RET*-mutant medullary thyroid cancer (MTC). Only second line indications are now targeted.

Design and conduct of clinical studies

Study LIBRETTO-001 is a phase I/II multi cohort study. The trial was initially designed as two parts (dose escalation and expansion) Phase I study. The update into the current design Phase I/ Phase II was done in the Protocol version 5.0 dated 30 May 2018 based on the results of the Phase I.

The main limitation of this clinical trial is its non-randomised nature and the lack of a control arm, in addition to the fact that this is the only clinical trial in support of this submission. These limitations could be considered acceptable by the CHMP in the context of a CMA when the effect observed is considered outstanding and all the requirements for a CMA are fulfilled.

Efficacy data and additional analyses

RET-fusion positive NSCLC

The evidence supporting the claimed indication in NSCLC came mostly from the 105 patients from the PAS (2L+ NSCLC setting). An integrated analysis set (IAS) was also performed, including PAS patients and those enrolled after the 105th patient but on or before the data cut-off (n=218). From a demographical point of view, the study population is considered representative of the intended population in NSCLC with most enrolled patients being metastatic and with an important disease burden.

Prior platinum chemotherapy

At the 16 December 2019 data cut-off date, results for the PAS population showed an ORR of 63.8% (67/105; 95% CI 53.9, 73) by IRC assessment. ORR as assessed by the investigator was consistent with the primary analysis (69.5% [95% CI: 59.8, 78.1]) with a concordance rate of 83%. The median DoR was 17.5 months (95% CI: 12.0, NE), with a median follow-up of 12.1 months. These results were confirmed at the 30 March 2020 with a median duration of follow-up of 15.67 months.

Considering the advanced stage of the disease (more than a half of the patients had received 3 or more prior regimens) this response rate can be considered of relevance.

Several exploratory analyses have been provided for ORR and DoR showing that in almost all subgroups, median duration of response was similar to that of the overall population.

CNS metastasis are common in lung cancer patients. From the 253 RET fusion positive NSCLC patients (independent of analysis set), 96 had CNS metastasis and 23 had measurable CNS lesions according to IRC assessment. The ORR in the evaluable patients was 87% (20/23; 95% CI: 66.4, 97.2). The DOR was 9.36 months (range: 2.8- 23.9+). These data, show the potential activity of selpercatinib on the

CNS, however, although data are promising, they should be interpreted with caution due to the small sample size.

The IAS population includes 184 efficacy evaluable patients. On 184 patients the ORR (IRC assessment) was 56.5% (95% CI: 49.0, 63.8) at the 16 December 2019 DCO. The median DoR was of 17.51 months (95% CI: 12.1, NE), with 24% of events and a median follow-up of 9.23 months. ORR according to the investigator was 62.5% (95% CI: 55.1, 69.5). The median PFS was 19.32 months (95% CI: 13.9, NE). At the 30 March 2020 DCO, the IAS population includes 218 efficacy evaluable patients, the ORR (IRC assessment) as 56.9% (95% CI: 50.0, 63.6). The median DoR was of 17.5 months (95% CI: 12.5, NE) with a median follow-up of 11.9 months.

RET-fusion positive TC

The applied indication is for the treatment of patients with RET fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior treatment (Cohort 1). As per inclusion criteria, patients in Cohort 1 must have failed or be intolerant to prior treatment with sorafenib and/or lenvatinib and must also be radioactive iodine-refractory as appropriate.

The total number of patients supporting the claimed indication in RET-fusion positive TC population was 27. Nineteen (19) out of them had received at least one prior systemic therapy other than RAI and 8 were treatment naïve (no other systemic therapy other than RAI). Thus, these 19 patients may be considered the target population. RET-fusion positive TC population was not hypothesized as PAS.

This population is comprised of patients with thyroid cancer of different histologies and whose management in clinical practice may differ. In this sense, while differentiated and poorly differentiated thyroid cancer in addition to Hurthle cell thyroid cancer may follow a similar approach, anaplastic thyroid cancer represents an aggressive tumour, with a very poor prognosis and whose management is quite different (ESMO 2019). Efficacy data according to histology have been provided and support consistency of effect across different histologies (data not shown).

At the 30 March 2020 DCO with an additional 9.5 months of follow-up (20.27 months in total), the ORR (IRC assessment) in the 19 patients initially enrolled was 78.9% (15/19) (95% CI: 54.4, 93.9). ORR by the investigator was 57.9% (11/15) (95% CI: 33.5, 79.7). A great difference percentage-wide between the IRC and the investigator in terms of ORR is still observed. The median DoR was 18.43 months (95% CI: 7.6, NE. Even though responses in this patient population appear durable the CI is wide, probably due to the low number of events/patients. Median PFS was 20.07 months (95% CI: 9.4, NE) and median OS was 27.20 (95% CI: 25.2, NE).

At the 30 March 2020 data cut-off, efficacy data for 3 additional efficacy eligible patients (22 total patients) was available. In this patient population, ORR (IRC assessment) was 77.3% (17/22) (95% CI: 54.6, 92.2).

RET-mutant MTC

The evidence supporting of the claimed indication in MTC came from 55 patients from the PAS (2L+ MTC setting) and 88 supportive patients from SAS1 subset (1L and 2L+ MTC setting, 16 and 72 patients, respectively). In addition, an IAS including all patients who met PAS criteria and were enrolled up to the data cut-off, was also performed (n=124). The sample size is considered limited to generate evidence in the full claimed indication for MTC.

No overall differences were observed in the treatment emergent adverse events or effectiveness of selpercatinib between patients who were ⩾65 years of age and younger patients. Limited data are available in patients ⩾75 years.

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. 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, two global phase 3 studies were projected to begin in December 2019 and to complete enrolment by July 2021 (LIBRETTO 431 in RET fusion-positive NSCLC) and August 2023 (LIBRETTO 531 in RET-mutant MTC).

These phase 3 studies will be conducted in patients with treatment-naive *RET*-fusion non-squamous NSCLC and previously untreated *RET*-mutant MTC. As of 3 August 2020, 12 patients had been enrolled in the LIBRETTO-431 and 7 patients in the LIBRETTO-531. No additional trials are planned in patients with RET-fusion positive thyroid cancer.

2.5.4. Conclusions on the clinical efficacy

The claimed indications in the context of this application for a CMA are as follows:

Retsevmo as monotherapy is indicated for the treatment of adults with:

- advanced RET fusion positive non small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy
- advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib

The unmet medical need in the applied indications is recognized.

Major therapeutic advantage (MTA) can be considered demonstrated for RET-mutant MTC patients who have failed prior treatment with cabozantinib and/or vandetanib as well as for those patients with RET fusion-positive thyroid cancer who had received prior systemic therapy with MKIs, as treatment options in these settings are rather limited or even lacking.

Regarding RET fusion-positive NSCLC, treatment options after progression on platinum-based therapy include immune checkpoint inhibitors as monotherapy (pembrolizumab, nivolumab, atezolizumab), single agent chemotherapy, or docetaxel in combination with ramucirumab or nintedanib. ORR in this setting range between 5-23% with chemotherapy and 14-21% with immunotherapy (DoR around 16-17 months with immunotherapy). However, it should be pointed out that all these regiments have demonstrated a clinical benefit in terms of PFS/OS. Data in patients with RET fusion-positive NSCLC even though limited, suggest response rate of these second line regimens could vary from 6-38%, which is lower than the reported ORR for selpercatinib. In this regard, in the study LIBRETTO-001 similar results were observed in an intrapatient analysis, which provides further insights on the apparently low response of immune and immune-chemotherapy in RET fusion-positive tumours.

A MTA of selpercatinib in RET fusion-positive NSCLC patients can therefore be considered demonstrated after immunotherapy and/or platinum-based chemotherapy.

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 fusion-positive NSCLC, the MAH should submit the clinical study report of the Phase 3 study J2G-MC-JZJC (LIBRETTO-431) comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC. The CSR should be submitted by 31 October 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

2.6. Clinical safety

Analysis of clinical safety data is based on LOXO-RET-17001 ("LIBRETTO-001"), "A Phase 1/2 study of oral LOXO-292 in patients with advanced solid tumours, including RET Fusion-positive Solid Tumours,

Medullary Thyroid Cancer, and Other Tumours with RET Activation". This study included a dose escalation (Phase 1) and dose expansion (Phase 2) portion.

This clinical trial was initiated in May of 2017 and is currently ongoing. Patients were treated with selpercatinib at doses ranging from 20 mg once daily (QD) through 240 mg BID during Phase 1. The RP2D was selected to be 160 mg BID.

Several pharmacology studies (listed below) have contributed to the safety dataset.

In addition, data from an expanded access programme, consisting of single-patient protocols, for a subset of patients who completed these studies (i.e., stopped selpercatinib after successful surgery; withdrew consent; progressed) and for whom clinical study reports were therefore available, have been provided.

Table 52. Clinical Pharmacology Studies Contributing Patient Data to the safety database

Study Number	Study Title	Number of Patients
LOXO-RET-18014	A 2-Part, Open-Label, Fixed-Sequence Study to Evaluate the Effects of Multiple Doses of Itraconazole and Rifampin on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects	24
LOXO-RET-18015	An Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects	20
LOXO-RET-18016	A Phase 1, Open-label, Two-part Study to Investigate the Absorption, Metabolism, Excretion, and Absolute Bioavailability of [14C]-LOXO-292 in Healthy Male Subjects	12
LOXO-RET-18017	An Open-Label, Fixed-Sequence Study to Evaluate the Effect of Multiple Doses of LOXO- 292 on the Single Dose Pharmacokinetics of Midazolam in Healthy Adult Subjects	16
LOXO-RET-18026	An Open-Label, Fixed-Sequence Study to Evaluate the Effect of Multiple Doses of LOXO-292 on the Single Dose Pharmacokinetics of Repaglinide in Healthy Adult Subjects	16
LOXO-RET-18032	A Single-Dose, Randomized, Double-Blind, Placebo- and Positive Controlled, 4 Way Crossover Study to Evaluate the Effect of LOXO-292 on the QTc Interval in Healthy Adult Subjects	32
LOXO-RET-18057	A Phase I, Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LOXO-292 in Healthy Adult Subjects	18
LOXO-RET-19075	An Open-Label, 3-Period, Fixed Sequence Study to Evaluate the Effect of an H2 Antagonist and a Proton Pump Inhibitor on the Single Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects	20

Three analysis sets were utilized for the analysis and interpretation of the safety data, as outlined below:

- The Overall Safety Analysis Set (OSAS, n = 746) includes all patients who were enrolled in LIBRETTO-001 and received 1 or more doses of selpercatinib as of the 30 Mars 2020 data cutoff date.

- The RET Fusion-positive NSCLC Safety Analysis Set (n =345) includes all patients with documented RET fusion-positive NSCLC who were enrolled in LIBRETTO-001 and received 1 or more doses of selpercatinib as of the 30 Mars 2020 data cutoff date.

-The RET-mutant MTC Safety Analysis Set (n = 315) includes all patients with documented RET-mutant MTC who were enrolled in LIBRETTO-001 and received 1 or more doses of selpercatinib as of the 30 March 2020 data cutoff date.

- The RET Fusion-positive Thyroid cancer Safety Analysis Set (n=42)

The OSAS included, in addition to the patients in the RET-mutant MTC and RET fusion-positive NSCLC analysis sets, 42 additional patients (28 patients with RET fusion-positive cancers other than thyroid or lung, and 16 patients with other cancers).

Patient exposure

At the 30 Mars 2020 data cutoff, the LIBRETTO-001 study was ongoing. Most patients were still being treated and new patients were still being enrolled. As of the data cutoff, 746 patients had received at least 1 dose of selpercatinib.

Table 53. Patient Disposition

	NSCLC (N=345) n (%)	MTC (N=315) n (%)	F+ TC (N=42) n (%)	Total (N=746) n (%)
Treatment Status (n, %)				
Discontinued	107 (31.0)	54 (17.1)	8 (19.0)	188 (25.2)
Continuing	238 (69.0)	261 (82.9)	34 (81.0)	558 (74.8)
Reason Treatment Discontinued (n, %)				
Progressive Disease	65 (18.8)	25 (7.9)	4 (9.5)	109 (14.6)
Adverse Event	23 (6.7)	14 (4.4)	1 (2.4)	41 (5.5)
Significant Noncompliance to Protocol	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.1)
Withdrawal of Consent	9 (2.6)	4 (1.3)	1 (2.4)	14 (1.9)
Death	6 (1.7)	5 (1.6)	0 (0.0)	11 (1.5)
Other	4 (1.2)	3 (1.0)	1 (2.4)	8 (1.1)
Intercurrent Illness Compromising Ability to Fulfill Protocol Requirements	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Requirement for Alternative Treatment per Investigator	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Study Status (n, %)				
Discontinued	77 (22.3)	40 (12.7)	8 (19.0)	140 (18.8)
Continuing	268 (77.7)	275 (87.3)	34 (81.0)	606 (81.2)
Reason Study Discontinued (n, %)				
Withdrawal of Consent	21 (6.1)	10 (3.2)	2 (4.8)	33 (4.4)
Death	55 (15.9)	28 (8.9)	6 (14.3)	103 (13.8)
Lost to Follow-up	1 (0.3)	1 (0.3)	0 (0.0)	3 (0.4)
Other	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Time on Treatment (TOT) (months) [2]				
n	345	315	42	746
Mean (SD)	11.16 (7.14)	12.47 (7.29)	13.10 (7.82)	11.65 (7.34)
Median	10.51	11.99	12.91	11.07
Min-Max	0.10-34.50	0.20-33.31	0.85-30.75	0.03-34.50
Time on Study (TOS) (months) [3]				
n	345	315	42	746
Mean (SD)	12.09 (6.90)	12.96 (7.16)	13.70 (8.25)	12.41 (7.21)
Median	11.07	12.42	13.49	11.71
Min-Max	0.20-34.50	0.39-33.31	0.85-30.75	0.03-34.50

Adverse events

Overall safety is summarized in the table below. Most treated patients (99.2%) experienced at least 1 treatment-emergent adverse event (TEAE) of any grade, regardless of relationship to study drug during the study and most patients (92.5%) had at least 1 TEAE that was attributed by the investigator to selpercatinib. More than half of the patients (59.7%) had Grade 3 or higher TAEs, 32.0 % considered related to selpercatinib.

Table 54. Summary of Safety Trends

	NSCLC (N=345)	MTC (N=315)	F+ TC (N=42)	Total (N=746)
Patients with TEAEs	344 (99.7)	313 (99.4)	42 (100.0)	740 (99.2)
Patients with TEAEs and Related to LOXO-292	322 (93.3)	293 (93.0)	41 (97.6)	690 (92.5)
Patients with TEAEs Maximum Severity 3 or 4	211 (61.2)	188 (59.7)	25 (59.5)	445 (59.7)
Patients with TEAEs Maximum Severity 3 or 4 and Related to LOXO-292	119 (34.5)	96 (30.5)	13 (31.0)	239 (32.0)
Patients with Serious TEAEs	136 (39.4)	97 (30.8)	14 (33.3)	262 (35.1)
Patients with Serious TEAEs and Related to LOXO-292	39 (11.3)	20 (6.3)	1 (2.4)	62 (8.3)
Patients with Fatal TEAEs	13 (3.8)	8 (2.5)	1 (2.4)	25 (3.4)
Patients with Fatal TEAEs and Related to LOXO-292	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with TEAEs and Action Taken of LOXO-292 Permanently Discontinued	25 (7.2)	15 (4.8)	2 (4.8)	45 (6.0)
Patients with TEAEs and Action Taken of LOXO-292 Permanently Discontinued and Related to LOXO-292	10 (2.9)	6 (1.9)	0 (0.0)	16 (2.1)

Cutoff Date: 2020-03-30.

Common adverse events

Table 55. Overall Incidence of TEAEs in ⩾15% of Patients in Decreasing Order of Frequency

MedDRA Preferred Term	All Patients (N=746)			
	TEAEs	Drug-Related TEAEs	TEAEs of Severity Grade ≥3	Drug-Related TEAEs of Severity Grade ≥3
Patients with any TEAEs, n (%)	**740 (99.2)**	**690 (92.5)**	**470 (63.0)**	**239 (32.0)**
Dry mouth	300 (40.2)	265 (35.5)	0 (0.0)	0 (0.0)
Diarrhoea	289 (38.7)	163 (21.8)	26 (3.5)	12 (1.6)
Hypertension	273 (36.6)	190 (25.5)	143 (19.2)	93 (12.5)
Aspartate aminotransferase increased	243 (32.6)	196 (26.3)	62 (8.3)	47 (6.3)
Alanine aminotransferase increased	243 (32.6)	197 (26.4)	73 (9.8)	60 (8.0)
Fatigue	233 (31.2)	144 (19.3)	11 (1.5)	8 (1.1)
Constipation	202 (27.1)	97 (13.0)	4 (0.5)	2 (0.3)
Oedema peripheral	192 (25.7)	108 (14.5)	2 (0.3)	0 (0.0)
Headache	176 (23.6)	65 (8.7)	11 (1.5)	3 (0.4)
Nausea	175 (23.5)	75 (10.1)	5 (0.7)	2 (0.3)
Blood creatinine increased	154 (20.6)	88 (11.8)	1 (0.1)	0 (0.0)
Abdominal pain	148 (19.8)	45 (6.0)	14 (1.9)	1 (0.1)
Rash	140 (18.8)	87 (11.7)	3 (0.4)	3 (0.4)
Electrocardiogram QT prolonged	133 (17.8)	103 (13.8)	30 (4.0)	21 (2.8)
Cough	121 (16.2)	9 (1.2)	0 (0.0)	0 (0.0)
Vomiting	121 (16.2)	32 (4.3)	7 (0.9)	1 (0.1)
Dyspnoea	115 (15.4)	13 (1.7)	19 (2.6)	0 (0.0)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients treated; n = number of patients in specific category; TEAE = treatment-emergent adverse event.

Notes: Percentage is calculated using the number of patients in the column heading as the denominator. TEAEs are defined as adverse events that started on or after the first administration of study drug. Patients are counted once within each preferred term. Patients with multiple severity ratings for a given AE are counted once under the maximum severity. Related events are those judged by the investigator as related to the study drug. Severity grade assignment based on CTCAE version 4.03: Grade 3 (severe), Grade 4 (life-threatening/debilitating), Grade 5 (fatal). Reported AE terms were coded using MedDRA version 21.0.

The most common Grade 3-4 events were hypertension (19.2% ; 12.5% related), ALT increase (9.8%; 8% related), AST increase (8.3%; 6.3% related)

Adverse drug reactions

The ADRs reported in the 746 patients treated with selpercatinib are shown in the below table.

Table 56. Adverse Drug Reactions in Patients Receiving Single Agent Selpercatinib (LIBRETTO-001)

System Organ Class	ADR	Selpercatinib (N=746)	
		All Grades Toxicity (%)	Grade 3, 4 Toxicity (%)

Immune system disorders[a]	*Common* Hypersensitivity[c]	 5.2	 1.7*
Metabolism and nutrition disorders	*Very common* Decreased appetite	 14.1	 0.1*
Nervous system disorders	*Very common* Headache[c] Dizziness[c]	 24 14.6	 1.5* 0.1*
Cardiac disorders	*Very common* Electrocardiogram QT prolonged[c]	 18.1	 4.0
Vascular disorders	*Very common* Hypertension[c]	 37.4	 19.4
Gastrointestinal disorders	*Very common* Abdominal pain[c] Diarrhoea[c] Nausea Vomiting Constipation Dry Mouth[c]	 25.5 39.0 23.5 16.2 27.1 40.3	 1.9* 3.5* 0.7* 0.9* 0.5* 0
Skin and subcutaneous tissue disorders	*Very common* Rash[c]	 28.7	 0.7*
General disorders and administration site conditions	*Very common* Pyrexia Fatigue[c] Oedema[c]	 14.3 38.2 38.7	 0.1* 2.3* 0.5*
Investigations[b]	*Very common* ALT Increased AST Increased Platelets Decreased Lymphocyte Count Decreased Magnesium Decreased Creatinine Increased	 49.5 55.0 34.5 46.2 25.6 39.1	 10.6 9 3.0 16.1 0.5 1.2
Blood and Lymphatic System	*Very common* Haemorrhage[d]	 16.6	 2.4

[a] Hypersensitivity reactions were characterized by a maculopapular rash often preceded by a fever with associated arthralgias/myalgias during the patient's first cycle of treatment (typically between Days 7-21).
[b] Based on laboratory assessments. Only patients with baseline and at least one post-baseline result are included.
[c] Consolidated terms
[d] See Description of selected adverse reactions for further characterisation.
*Only includes a grade 3 adverse reaction.

Serious adverse event/deaths/other significant events

Deaths

The table below provides a summary of deaths occurred in Libretto-001 study for all patients in the Safety Population.

Table 57. Summary of death occurred in Libretto-001 study, at the time of cut-off (Safety Analysis Set) - LIBRETTO-001 (Data Cut-off: 30 March 2020)

NSCLC	MTC	F+ TC	Total
	(N=345)	(N=315)	(N=42)	(N=746)
Within 28 Days of Last Dose	55 (15.9)	28 (8.9)	6 (14.3)	103 (13.8)
Disease Progression	36 (10.4)	18 (5.7)	5 (11.9)	70 (9.4)
Adverse Event	13 (3.8)	8 (2.5)	1 (2.4)	25 (3.4)
Other	6 (1.7)	2 (0.6)	0 (0.0)	8 (1.1)
More than 28 Days after Last Dose	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Disease Progression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse Event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)

One hundred and four subjects (13.9%, 104/746) in the safety population had died at the time of data cut-off date: 56 patients with RET fusion-positive NSCL, 28 with RET mutant MTC and 14 with other tumour RET alteration. In most cases (67.3%, n=70) the reported reason for death was disease progression followed by Adverse event (24%, n=25) then other (8.6%, n=9).

One hundred and three (99%, 103/104) of patients died either while receiving selpercatinib or within 28 days of their last dose. The reported reason for death was disease progression (67.9%, 70/103) followed by adverse event (24.3%, 25/103) then other (~0.8, 8/103). Although the population is too small to draw any precise conclusions, it is noted that the number of deaths is higher in NSCL patients (~54% , 55/103) than in the MTC population (27%, 28/103).

Serious Adverse Events

A total of 262 (35.1%) of the 746 patients experienced a treatment-emergent serious adverse event (SAE).

Table 58. Overall Incidence of SAEs in ⩾1% of Patients in decreasing order of frequency (Safety Analysis Set) - LIBRETTO-001 (Data Cut-off: 30 March 2020)

MedDRA Preferred Term	All Patients (N=746)	
	Total Patient Incidence of Treatment-Emergent SAEs by Frequency (≥1% patients)	Total Patient Incidence of Treatment-Related Treatment-Emergent SAEs
Patients with any SAEs n (%)	262 (35.1)	**62 (8.3)**
Pneumonia	23 (3.1)	0
Dyspnoea	14 (1.9)	0
Hyponatraemia	14 (1.9)	0
Alanine aminotransferase increased	12 (1.6)	9 (1.2)
Aspartate aminotransferase increased	12 (1.6)	9 (1.2)
Abdominal pain	11 (1.5)	2 (0.3)
Pleural effusion	11 (1.5)	0
Drug hypersensitivity	10 (1.3)	10 (1.3)
Diarrhoea	9 (1.2)	3 (0.4)
Acute kidney injury	8 (1.1)	0
Pyrexia	8 (1.1)	2 (0.3)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients treated; n = number of patients in specific category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Notes: Percentage is calculated using the number of patients in the column heading as the denominator. TEAEs are defined as AEs that started on or after the first administration of study drug. Patients are counted once within each preferred term. Reported AE terms were coded using MedDRA version 21.0.

Approximately 35% of subjects in the safety population experienced at least one SAE and only 8.3% were adjudicated as treatment-related by the Investigator. Although this could be considered overall reassuring, the absence of direct controls and the heterogeneity of the safety population limit the reliability of causality relationships.

Adverse events of special interest

Three adverse events of special interest (AESI) identified early in the clinical programme were ALT or AST increase, drug hypersensitivity, and hypertension by aggregating composite terms. All of these AEs are monitorable and are reversible with dose interruptions, reductions, or discontinuations.

AST/ALT Increase

Based on laboratory assessment, ALT and AST elevations were reported in 49.5% and 55% patients, respectively. Grade 3 or 4 ALT or AST elevations were reported in 10.6% and 9.0% patients respectively.

The median time to first onset was: AST increase 4.1 weeks (range: 0.7, 108.1), ALT increase 4.1 weeks (range: 0.9, 111.1).

Hypertension

In patients receiving selpercatinib, the median maximum increase from baseline systolic pressure was 29 mm Hg (range: −11, +96). Only 13% of patients retained their baseline grade during treatment, 45% had an increasing shift of 1 grade, 32.7% of 2 grades, and 8.3% of 3 grades. Hypertension was reported in 41.9% patients with history of hypertension (26.9% with grade 3) and 34.2% of patients without history of hypertension (14.1% with grade 3, 4).

Overall, a total of 19.4% displayed treatment emergent Grade 3 hypertension (defined as maximum systolic blood pressure greater than 160 mm Hg). Diastolic blood pressure results were similar, but the increases were of lesser magnitude. No patients were permanently discontinued due to hypertension.

Other Notable Event:

QT prolongation

Review of ECG data showed 6.2% of patients had >500 msec maximum post baseline QTcF value, and 17.5% of patients had a >60 msec maximum increase from baseline in QTcF intervals. At the time of the last post-baseline measurement, increase in QTc value >60 msec was reported in 2.6% of patients.

There were no reports of Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, or ventricular flutter. No patient discontinued treatment due to QT prolongation.

Haemorrhages

Grade ≥3 haemorrhagic events occurred in 2.4% of patients treated with selpercatinib, including 3 (0.4%) patients with fatal haemorrhagic events, one case each of cerebral haemorrhage, tracheostomy site haemorrhage, and haemoptysis. The median time to onset was 12.8 weeks (range: 0.1 week to 124.3 weeks).

Laboratory findings

Table 59. TEAEs by Aggregating Composite Term (Safety Analysis Set) - LIBRETTO-001 (Data Cut-off: 30 March 2020)

AE Category Meddra Preferred Term	NSCLC (N=345)				MTC (N=315)				F+ TC (N=42)				Total (N=746)			
	Any Grade		Grade 3/4/5		Any Grade		Grade 3/4/5		Any Grade		Grade 3/4/5		Any Grade		Grade 3/4/5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Alanine aminotransferase increased	129	(37.4)	44	(12.8)	87	(27.6)	22	(7.0)	10	(23.8)	2	(4.8)	243	(32.6)	73	(9.8)
Alanine aminotransferase increased	129	(37.4)	44	(12.8)	87	(27.6)	22	(7.0)	10	(23.8)	2	(4.8)	243	(32.6)	73	(9.8)
Aspartate aminotransferase increased	131	(38.0)	35	(10.1)	89	(28.3)	19	(6.0)	9	(21.4)	3	(7.1)	243	(32.6)	62	(8.3)
Aspartate aminotransferase increased	131	(38.0)	35	(10.1)	89	(28.3)	19	(6.0)	9	(21.4)	3	(7.1)	243	(32.6)	62	(8.3)
Blood creatinine increased	71	(20.6)	5	(1.4)	91	(28.9)	4	(1.3)	8	(19.0)	0	(0.0)	179	(24.0)	10	(1.3)
Blood creatinine increased	64	(18.6)	1	(0.3)	77	(24.4)	0	(0.0)	6	(14.3)	0	(0.0)	154	(20.6)	1	(0.1)
Electrocardiogram QT prolonged	61	(17.7)	17	(4.9)	63	(20.0)	11	(3.5)	4	(9.5)	2	(4.8)	135	(18.1)	30	(4.0)
Electrocardiogram QT prolonged	61	(17.7)	17	(4.9)	61	(19.4)	11	(3.5)	4	(9.5)	2	(4.8)	133	(17.8)	30	(4.0)
Electrocardiogram QT interval abnormal	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.3)	0	(0.0)

Cutoff Date: 2020-03-30.
Percentage is calculated using the number of patients in the column heading as the denominator.
Treatment-emergent Adverse Events (TEAEs) are defined as adverse events that start on or after the first administration of LOXO-29
Reported adverse event terms were coded using MedDRA (version 21.0).
Severity grade assignment based on CTCAE (v4.03): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening/ debilitating), Grade 5 (fatal).

Electrocardiograms

Electrocardiogram QT prolonged was a notable AE that was reported in 135 (18.1%) patients, of which 30 (4.0%) had events ≥Grade 3. No patient discontinued treatment due to QT prolongation. Sixteen (2.1%) patients had dose interruption and 19 (2.5%) patients had dose reduction due to QT prolongation.

Safety in special populations

Table 60. Safety Analysis by Categorical Age Group - LIBRETTO-001 (Data Cut-off: 30 March 2020)

MedDRA Terms	Age <65 (N = 494)	Age 65-74 (N = 183)	Age 75-84 (N = 61)	Age 85+ (N = 8)
Total AEs	488 (98.8)	183 (100.0)	61 (100.0)	8 (100.0)
Serious AEs – total[a]	147 (29.8)	79 (43.2)	31 (50.8)	5 (62.5)
Fatal	13 (2.6)	7 (3.8)	5 (8.2)	0 (0.0)
Hospitalisation/prolong existing hospitalisation	140 (28.3)	78 (42.6)	29 (47.5)	5 (62.5)
Life-threatening	18 (3.6)	12 (6.6)	6 (9.8)	0 (0.0)
Disability/incapacity	3 (0.6)	1 (0.5)	1 (1.6)	0 (0.0)
Other (medically significant)	24 (4.9)	12 (6.6)	5 (8.2)	0 (0.0)
AE leading to drop-out	16 (3.2)	11 (6.0)	8 (13.1)	1 (12.5)
Adverse events of special interest				
ALT elevations[b]	240 (48.6)	95 (51.9)	23 (37.7)	7 (87.5)
AST elevations[b]	253 (51.2)	108 (59.0)	38 (62.3)	6 (75.0)
ALP elevations[b]	176 (35.6)	70 (38.3)	22 (36.1)	3 (37.5)
Total bilirubin elevations[b]	118 (23.9)	40 (21.9)	21 (34.4)	2 (25.0)
Hypertension	181 (36.6)	69 (37.7)	24 (39.3)	5 (62.5)
QT prolongation	77 (15.6)	38 (20.8)	17 (27.9)	3 (37.5)
Psychiatric disorders[c]	105 (21.3)	49 (26.8)	17 (27.9)	4 (50.0)
Nervous system disorders[c]	247 (50.0)	97 (53.0)	37 (60.7)	3 (37.5)
Cardiac disorders[c]	62 (12.6)	28 (15.3)	15 (24.6)	2 (25.0)
Vascular disorders[c]	207 (41.9)	83 (45.4)	30 (49.2)	4 (50.0)
Infections and infestations[c]	250 (50.6)	99 (54.1)	35 (57.4)	5 (62.5)
Cerebrovascular disorders[d]	12 (2.4)	10 (5.5)	5 (8.2)	0 (0.0)
Quality of life decreased[e]	5 (1.0)	2 (1.1)	1 (1.6)	1 (12.5)
Accidents and injuries[d]	57 (11.5)	26 (14.2)	14 (23.0)	2 (25.0)
Anticholinergic syndrome[d]	306 (61.9)	115 (62.8)	46 (75.4)	7 (87.5)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[f]	79 (16.0)	43 (23.5)	16 (26.2)	2 (25.0)

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; MedDRA = Medical Dictionary for Regulatory Activities ; N = number of patients treated; PT = Preferred Term; SMQ = Standardized MedDRA Query; ULN = upper level of normal.
Data cutoff date: 30 March 2020.
Reported adverse event terms were coded using MedDRA version 21.0.

a Subjects may be counted in more than 1 Serious AE subcategory.

b Source: Lab reports. Grade based on CTCAE (version 4.03). Potential Hy's Law case is defined as ALT or AST ≥3x ULN, Total Bilirubin >2x ULN and ALP <2x ULN.

c Selected based on System Organ Class (MedDRA version 21.0).

d Selected based on SMQ (MedDRA version 23.0).

e Change to ECOG 3 or 4 at any time during treatment.

f Searching PTs for this item are 'Orthostatic hypotension', 'Fall', 'Syncope', 'Loss of consciousness', 'Dizziness', 'Ataxia', 'Fracture', 'Wrist fracture', 'Spinal fracture', 'Ankle fracture', 'Hip fracture', 'Dizziness postural'.

Immunological events

Hypersensitivity

Hypersensitivity was analysed as a composite term including the MedDRA preferred terms (PTs) of 'hypersensitivity' and 'drug hypersensitivity.' Hypersensitivity occurred in a total of 5.2% (39/746) of patients receiving selpercatinib, including Grade 3 hypersensitivity in 1.7% (13/746) of patients. There were no hypersensitivity events of Grade 4 or Grade 5 severity. Thirty-one (4.2%) patients had hypersensitivity related to study drug. Fourteen (1.9%) patients had SAEs of hypersensitivity, all of which were related to the study drug. Of the 39 total patients with hypersensitivity (composite term), 26 patients (3.5%) underwent dose reduction, 6 patients (0.8%) underwent dose interruption, and 3 patients (0.4%) had study drug discontinuation as the most significant action taken.

In study LIBRETTO 001, 24.7% (184/746) of patients treated with selpercatinib had previously received anti PD 1/PD L1 immunotherapy. Of the 39 patients with hypersensitivity, 64.1% (25/39) had NSCLC and had received prior anti PD 1/PD L1 immunotherapy. Grade 3 hypersensitivity occurred in 3.8% (7/184) of the patients previously treated with anti PD 1/PD L1 immunotherapy. The median time to onset was 1.9 weeks (range: 0.9 week to 77 weeks): 1.7 weeks in patients with previous anti PD 1/PD L1 immunotherapy and 8.9 weeks in patients who were immunotherapy naïve.

Table 61. Summary of Hypersensitivity TEAEs - LIBRETTO-001 (Data Cut-off: 30 March 2020)

	Overall (N=746)
Number (%) of Patients with Hypersensitivity, n (%)[a,b]	
Any grade	39 (5.2)
Grade 1	7 (0.9)
Grade 2	19 (2.5)
Grade 3	13 (1.7)
Drug-Related AE	31 (4.2)
Serious AE	14 (1.9)
Drug-Related SAE	14 (1.9)
Dose Modification	
AEs Leading to Interruption	6 (0.8)
AEs Leading to Reduction	26 (3.5)
AEs Leading to Discontinuation	3 (0.4)
Time to First Onset, Weeks	
N	39
Mean (SD)	7.8 (14.68)
Median	1.9
Range	0.9, 77.0
Outcome of the Last Episode	
Recovered/Resolved	34 (4.6)
Not Recovered/Not Resolved	5 (0.7)

a Hypersensitivity is based on Composite Term.

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

Abbreviations: AE = adverse event; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event.

Safety related to drug-drug interactions and other interactions

No specific data on safety-related to DDI has been submitted (see section on clinical pharmacology).

Discontinuation due to adverse events

Forty-five patients (6.0%) permanently discontinued treatment because of an AE, with no predominant pattern among the specific AEs reported or any new safety concerns: 16 of the 45 patients (2.1% of all patients treated) discontinued selpercatinib because of a treatment-related AE.

Nine AEs led to treatment discontinuation in more than 1 patient:

- ALT increased and sepsis (3 patients each, 0.4%), and
- AST increased, cardiac failure, drug hypersensitivity, fatigue, pericardial effusion, pneumonia, and thrombocytopenia (2 patients each, 0.3%).

Two hundred fifty-one (33.6%) patients had dose reductions due to any AE. The most common TEAEs that led to dose reductions were

- ALT increase (53 patients, 7.1%)
- AST increase (48 patients, 6.4%)
- fatigue (20 patients, 2.7%)
- QT prolongation (19 patients, 2.5%), and
- drug hypersensitivity (17 patients, 2.3%).

Three hundred and thirty-four (44.8%) patients had dose interruptions due to any AE. The most common TEAEs that led to dose interruptions were

- ALT increase (42 patients, 5.6%)
- AST increase and hypertension (each in 37 patients, 5.0%)
- diarrhoea (24 patients, 3.2%)
- pyrexia (20 patients, 2.7%), and
- electrocardiogram (ECG) QT prolongation (16 patients, 2.1%).

Post marketing experience

No post marketing data have been submitted.

2.6.1. Discussion on clinical safety

The integrated safety database supporting the MAA of selpercatinib in the broad claimed indications is comprised of 746 subjects who received at least one dose of selpercatinib across a Phase I/II dose escalation/expansion study with a data cutoff of 30 March 2020.

As a general concern, the uncontrolled design of the study on which the analysis is based and the limited median exposure (11.07 months versus 5.9 months in the initial report) do not allow to clearly differentiate between signs/symptoms of the underlying malignancy and selpercatinib-related adverse events (AEs), further limiting precise evaluations of selpercatinib safety profile. The integrated safety population is also characterised by a significant heterogeneity between populations in terms of age (min 15, max 90 years), type of underlying malignancy, dose administered (from 20mg QD to 240mg BID), that further complicates safety evaluation.

The median treatment duration in adult patients was 11.7 months. The median time on treatment in MTC population was ~12 months vs 10.5 months in NSCLC.

Patients with hepatic, renal or cardiac impairment (including prolonged QT syndrome) at baseline were not included in LIBRETTO-001 (as per inclusion/exclusion criteria). Clinical pharmacology studies are ongoing to further investigate use in patients with renal and hepatic impaired patients. Exposure and safety in patients with severe hepatic impairment and cardiac impairment have been included as

missing information in the Risk management plan (RMP). There were also limited numbers of patients over 75 years of age.

The 5 most frequently reported AEs were dry mouth (35.5%), diarrhoea (21.8%), hypertension (25.5%), AST increase (26.3%), and ALT increase (26.4%). Grade≥3 AEs were reported in 59.7% of patients.

The most commonly reported Grade≥ 3 AEs were hypertension (19.2%) and ALT increased (9.8%). Apart from hypertension, most reported AEs which occurred in ≥ 15% of patients were Grades 1-2 in severity.

ALT and AST should be monitored prior to the start of selpercatinib therapy, every 2 weeks during the first 3 months of treatment, monthly for the next 3 months of treatment, and otherwise as clinically indicated. Based on the level of ALT or AST elevations, selpercatinib may require dose modification. Dose modification is recommended for patients who develop Grade 3 or 4 ALT or AST increase (see sections 4.2, 4.4 and 4.8 of the SmPC).

In view of the risk of hypertension, patient blood pressure should be controlled before starting selpercatinib treatment, monitored during selpercatinib treatment and treated as needed with standard anti-hypertensive therapy. Based on the level of increased blood pressure, selpercatinib may require dose modification. Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled with antihypertensive therapy (see sections 4.2, 4.4 and 4.8 of the SmPC).

QT interval prolongation was reported in patients receiving selpercatinib. Therefore, dose interruption or modification may be required in patients (see sections 4.2 and 4.4). Selpercatinib should be used with caution in patients with such conditions as congenital long QT syndrome or acquired long QT syndrome or other clinical conditions that predispose to arrhythmias.

Patients should have a QTcF interval of ≤470 ms and serum electrolytes within normal range before starting selpercatinib treatment. Electrocardiograms and serum electrolytes should be monitored in all patients after 1 week of selpercatinib treatment, at least monthly for the first 6 months and otherwise, as clinically indicated, adjusting frequency based upon risk factors including diarrhoea, vomiting, and/or nausea. Hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiating selpercatinib and during treatment. Selpercatinib may require dose interruption or modification (see sections 4.2, 4.4 and 4.8 of the SmPC).

Serious including fatal haemorrhagic events were reported in patients receiving selpercatinib. Selpercatinib should be permanently discontinued in patients with severe or life threatening haemorrhage (see sections 4.2, 4.4 and 4.8 of the SmPC).

There are no available data from the use of selpercatinib in pregnant women. Studies in animals have shown reproductive toxicity. Selpercatinib is not recommended during pregnancy. Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose of selpercatinib. Men with female partners of childbearing potential should use effective contraception during treatment and for at least one week after the last dose of selpercatinib.

It should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

It is unknown whether selpercatinib is excreted in human milk. A risk to breast-fed newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with selpercatinib and for at least one week after the last dose.

No human data on the effect of selpercatinib on fertility are available. Based on findings from animal studies, male and female fertility may be compromised by treatment with selpercatinib. Both men and

women should seek advice on fertility preservation before treatment (see sections 4.4 and 4.6 of the SmPC).

Selpercatinib may have minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience fatigue or dizziness during treatment with selpercatinib (see sections 4.7 and 4.8 of the SmPC).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

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 studies LIBRETTO-431 and LIBRETTO-531 will allow a contextualisation of the safety data compared to the control arm.

2.6.2. Conclusions on the clinical safety

The safety database includes 746 patients treated with selpercatinib. Selpercatinib presents substantial toxicity, as shown by the high incidence of severe, including life-threatening and fatal adverse events. The safety profile is nevertheless consistent with that seen for other TKIs, with significant gastrointestinal toxicities, hypertension, increased transaminases and QT interval prolongation. Haemorrhages, including Cerebrovascular Accident (CVA), CNS haemorrhage, and cardiac toxicity (other than QT interval prolongation). Relevant information has been reflected in sections 4.4 and 4.8 of the SmPC.

Based on available data, the safety profile of selpercatinib in adult patients is considered overall manageable. Uncertainties are still present due to the lack of direct controls and heterogeneity of patients which will be addressed by the specific obligations being imposed in the context of the CMA.

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 fusion-positive NSCLC, the MAH should submit the clinical study report of the Phase 3 study J2G-MC-JZJC (LIBRETTO-431) comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC. The CSR should be submitted by 31 October 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.

2.7. Risk Management Plan

Safety concerns

Table 62. Summary of the 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 beyond adverse reactions reporting and signal detection:

In addition to routine pharmacovigilance activities, specific follow-up forms are used to collect additional scientific/medical data to facilitate evaluation of cases. The follow-up forms listed here are only related to the currently listed safety concerns: liver injury, cardiac arrhythmia due to QT prolongation, and reproductive and developmental toxicities.

Follow-up forms:

- Pregnancy data collection form–maternal
- Pregnancy outcome form–maternal
- Pregnancy data collection form–paternal
- Pregnancy outcome form–paternal

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

Risk minimisation measures

Table 63. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Liver injury	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not Applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Studies: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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 **Additional risk minimisation measures:** Not Applicable	**Routine pharmacovigilance activities** **beyond adverse reactions reporting and** **signal detection:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Additional pharmacovigilance activities: Study: None

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

Plans for Post-Authorisation Efficacy Studies

Table 64. Planned and Ongoing Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorisation				
None				
Efficacy studies that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
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). **Status:** Ongoing	To evaluate the safety and tolerability of selpercatinib	Long Term efficacy,	First Patient Visit	May 2017
			Final Study Report	Estimated 31 December 2023
J2G-MC-JZJB A Multicentre, Randomized, Open-label, Phase 3 Trial Comparing Selpercatinib to Physicians Choice of Cabozantinib or Vandetanib in Patients with Progressive, Advanced, Kinase Inhibitor	To compare TFFS, PFS, and other efficacy outcomes of patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC treated with selpercatinib	Long-term efficacy,	First Patient Visit	February 2020
			Final Study Report	Estimated 28 February 2025

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Naïve, *RET*-Mutant Medullary Thyroid Cancer (LIBRETTO-531) **Status:** Ongoing	versus cabozantinib or vandetanib			
J2G-MC-JZJC LIBRETTO-431: A Multicentre, Randomized, Open-Label, Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab as Initial Treatment of Advanced or Metastatic *RET* Fusion-Positive Non-Small Cell Lung Cancer **Status:** Ongoing	To compare PFS and other efficacy outcomes of selpercatinib with platinum-based (carboplatin or cisplatin) and pemetrexed therapy with or without pembrolizumab in patients with advanced or metastatic *RET* fusion-positive NSCLC	Long-term efficacy,	First Patient Visit	March 2020
			Final Study Report	Estimated 31 October 2023
Protocol Number: **LOXO-RET-18036** A Phase 1/2 Study of the Oral RET Inhibitor LOXO-292 in Pediatric Patients with Advanced RET-Altered Solid or Primary Central Nervous System Tumours **Status:** Ongoing	To determine the objective response rate (ORR) and other efficacy outcomes in paediatric patients with advanced cancer harbouring an activating RET alteration following initiation of selpercatinib	Long-term efficacy in paediatric patients,	First Patient Visit	July 2019
			Final Study Report	Estimated 30 June 2023

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5, dated 4th December 2020, is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 08.05.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The CHMP, based on the available data, considers selpercatinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Retsevmo (selpercatinib) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under a conditional marketing authorisation [REG Art 14-a]

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Retsevmo as monotherapy is indicated for the treatment of adults with:

– advanced RET fusion positive non small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy

– advanced RET fusion positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

3.1.2. Available therapies and unmet medical need

According to ESMO and NCCN guidelines, the preferred standard of care in the second line setting, is systemic immune checkpoints inhibitors, such as nivolumab, pembrolizumab or atezolizumab, or other systemic therapy as docetaxel, pemetrexed or gemcitabine, among others.

Regarding the treatment of RET-mutant medullary thyroid cancer (MTC), there are currently two alternatives available: cabozantinib and vandetanib, as per ESMO and NCCN guidelines. These two drugs are MKIs that have demonstrated in RCTs a better efficacy profile in RET mutated patient compared to the overall MTC population. In patients who are refractory or intolerant to vandetanib or cabozantinib there are no approved treatment options.

There is no approved therapy for RET fusion-positive thyroid cancer (TC) after failure of one prior MKI. However, there are still alternatives available such as the use of subsequent MKIs after failure of a first line MKI which is not contraindicated in TC, although data on second line treatment are scarce and even more so in the RET fusion positive TC patients. There is a need for treatments showing efficacy in this patient population.

3.1.3. Main clinical studies

Data are mainly taken from study LOXO-RET-17001 (LIBRETTO-001), a multicentre, open-label, phase 1/2 study in patients with advanced solid tumours, including RET fusion-positive solid tumours (e.g., NSCLC, thyroid, pancreas, colorectal), RET-mutant MTC, and other tumours with RET activation (e.g., mutations in other tumour types or other evidence of RET activation). This study is ongoing and includes two parts: Phase 1 (dose escalation) and Phase 2 (dose expansion); the study is currently in Phase 2.

3.2. Favourable effects

RET-fusion positive NSCLC

Prior platinum chemotherapy

The ORR (IRC assessment) in the PAS population (n=105) was 63.8% (95% CI: 53.9, 73.0). The median DoR was 17.5 months (95% CI: 12.0, NE), with a median follow-up of 15.7 months. Regarding other secondary endpoints, median PFS was 19.25 months (95% CI: 13.9, NE), with a median follow-up of 16.76 months and around 48% of events reported. Median OS was not reached at the time of the DCO (27% of events observed).

In the IAS population there are 218 evaluable patients and the ORR (IRC assessment) was 56.9% (95% CI: 50.0, 63.6). Median DoR was of 17.51 months (95% CI: 12.1, NE), with a median follow-up of 11.9 months.. The median PFS was 19.29 months (95% CI: 16.5, NE). Median OS was not reached at the time of DCO.

RET-fusion positive TC

For the 19 patients initially enrolled, the ORR (IRC assessment) was 78.9% (15/19) (95% CI: 54.4, 93.9). The median DoR was 18.43 months (95% CI: 7.6, NE), with a median follow-up of 22.01 months. Median PFS was 20.07 months (95% CI: 9.4, NE) and median OS was 27.20 (95% CI: 25.3, NE). At the March 2020 DCO, a total of 22 evaluable patients have been enrolled. ORR in these 22 patients was 77.3% (95% CI: 54.6, 92.2).

RET-mutated MTC

Prior cabozantinib/vandetanib treatment

In PAS population (n=55), the ORR (IRC assessment) was 69.1% (95% CI: 55.2, 80.9%). At the time of the DCO, with a median follow-up of 17.45 months, median DoR was not reached (95% CI: 19.1, NE). Regarding other secondary endpoints, median PFS was not reached and median OS was of 33.25 months (95%CI: 33.2; NE).

In the IAS population as of the March 2020 data cut-off, the number of evaluable patients was of 143 and the ORR was 69.2% (95% CI: 61, 76.7). The median DoR was not reached (95% CI: 19.1, NE), with a median follow-up of 10.05 months. In line with the PAS population, median PFS was not reached at the time of the DCO and median OS was of 33.25 months (18% events).

3.3. Uncertainties and limitations about favourable effects

The main limitations 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.

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 2 randomised phase III trials: LIBRETTO-431 in patients with locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC and LIBRETTO-531 in patients with progressive, advanced, kinase inhibitor-naive, RET-mutant MTC.

3.4. Unfavourable effects

The safety database is comprised of 746 subjects who received at least one dose of selpercatinib across a Phase I/II dose escalation/expansion study with a data cut-off of 30 March 2020.

Grade ≥3 AEs and SAEs were experienced, respectively, by 63% and 35% of patients.

The most commonly reported ADRs were AST increased (55.0%), ALT increased (49.5%), lymphocyte count decreased (46.2%), dry mouth (40.3%), diarrhoea (39.0%), Oedema (38.7%), fatigue (38.2%) and hypertension (37.4%). The most common Grade ≥ 3 ADRs are hypertension (19.4%), lymphocyte count decreased (16.1%), ALT increased (10.6%), AST increased (9%)

The most commonly (≥1% of patients) reported SAEs by PT were pneumonia (3.1%), dyspnoea, and hyponatremia (each 1.9%). ALT increase, AST increase (each 1.6%), abdominal pain, pleural effusion (each 1.5%), drug hypersensitivity (1.3%), diarrhoea (1.2%), acute kidney injury and pyrexia (each 1.1%).

Grade 5 AEs occurred in 104 (13.9%, 104/746) patients, all in the adult population; none of which were assessed by the investigator as related to selpercatinib. The reported reason for 24.3% (25/103) of these early deaths is an adverse event.

The impact of selpercatinib on the incidence of QT interval prolongation was also confirmed: 18.1% of patients experienced this ADR, of which 30 (4.0%) had events ≥Grade 3. QT interval prolongation was managed by selpercatinib dose interruptions or reductions. No patient discontinued treatment due to QT prolongation.

As for other TKIs, the risk for haemorrhagic events and cardiac toxicity (other than QT interval prolongation) are of concern and considered as important identified risks (see RMP).

3.5. Uncertainties and limitations about unfavourable effects

The uncontrolled design of LIBRETTO-001 study and the limited median exposure (11.7 months) do not allow to clearly disentangle signs/symptoms of the underlying malignancy and selpercatinib-related adverse events (AEs), limiting precise evaluation of selpercatinib's safety profile. The integrated safety population is also characterised by a significant heterogeneity in terms of age (min 15, max 90 years), type of underlying malignancy, dose administered (from 20mg QD to 240mg BID), that further complicates safety evaluations.

Finally, long-term follow-up is needed as uncertainties still remain on the safety profile of selpercatinib. The updated data from the LIBRETTO-001 and the two randomised phase 3 studies (LIBRETTO-431 and LIBRETTO-531) to be submitted post approval will address these uncertainties.

3.6. Effects Table

Table 65. Effects Table for Selpercatinib (data cut-off: 30 March 2020)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects DCO March 2020						
RET-fusion positive NSCLC						
Prior Platinum Chemotherapy (PAS, n=105)						
ORR	rate	% (95% CI)	63.8 (53.9, 73.0)	NA		
DOR	median	Months (95% CI)	17.51 (12.1, NE)	NA		
PFS	median	months (95% CI)	19.25 (13.9, NE)	NA		
Follow up	median	months (25th, 75th Percentiles)	5.67 (12.1, 18.2)	NA		
Prior Platinum Chemotherapy (IAS, n=218)						
ORR	rate	% (95% CI)	56.9 (50.0.0, 63.6)	NA		
DOR	median	Months (95% CI)	17.51 (12.1, NE)	NA		
RET-mutant MTC						
Previously treated with cabozantinib or vandetanib (PAS, n=55)						
ORR	rate	% (95% CI)	69.1 (55.2, 80.9)	NA		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
DOR	median	Months (95% CI)	NE (19.1, NE)	NA		
Previously treated with cabozantinib or vandetanib (IAS, n=143)						
ORR	rate	% (95% CI)	69.2 (61.0, 76.7)	NA		
DOR	median	Months (95% CI)	NE (19.1, NE)	NA		
Previously treated RET-fusion positive TC *(PAS, n=19)*						
ORR	rate	% (95% CI)	78.9 (54.4, 93.9)	NA		
DOR	median	Months (95% CI)	18.43 (7.6, NE)	NA		
Unfavourable Effects DCO March 2020						
AE that led to treatment discontinuation		n (%)	45 (6.0)	NA		
Death due to AE		n (%)	25 (3.4)	NA		
SAEs		n (%)	262 (35.1)	NA		
Grade 3-4 AEs		n (%)	445 (59.7)	NA		

Abbreviations: NSCLC: Non-small cell lung cancer; MTC: Medullary thyroid cancer; DCO: Data cut-off; AE: AE: Adverse event; SAE: Serious adverse event. ORR: Overall response rate, DOR: Duration of response, PFS: Progression free survival.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results from study LIBRETTO-001 are considered promising and of clinical relevance in the applied indications, with response rates ranging from 56.9% to 78.9% and a minimum duration of response of 17.5 months depending on the indication and the patient population.

From a safety point of view, the most common AEs reported with selpercatinib were gastrointestinal (mainly diarrhoea and constipation), dry mouth, hypertension, fatigue and AST and ALT increases. ALT/AST increases, hypertension and hypersensitivity are considered adverse events of special interest for selpercatinib.

Uncertainties remain due to the lack of direct controls and population heterogeneity in the safety database.

3.7.2. Balance of benefits and risks

The effect observed with selpercatinib in the intended target populations is considered of clinical relevance.

Uncertainties are still present due to the lack of direct controls and population heterogeneity of the safety database and will be addressed by the studies imposed as specific obligations which will provide comprehensive data on both efficacy and safety aspects.

The benefit -risk balance for selpercatinib in the applied indications is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The 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 seriously debilitating, 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 the results from study LIBRETTO-001 are of clinical relevance in the applied indications, with response rates ranging from 56.9% to 78.9% and a minimum duration of response of 17.5 months depending on the indication and the patient population. From a safety point of view, the most common AEs reported with selpercatinib were gastrointestinal (mainly diarrhoea and constipation), dry mouth, hypertension, fatigue and AST and ALT increases. In view of the assumed clinical benefit, the safety of selpercatinib is considered acceptable.
- It is likely that the applicant will be able to provide comprehensive data.

Study J2G-MC-JZJC (LIBRETTO-431) is a global, multicentre, randomised (1:1), open- label, controlled Phase 3 study of selpercatinib compared to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC. Twenty-two (22) patients had been enrolled as of 27 October 2020, and 155 sites (71.4%) were enrolment ready. In addition, the number of pre-screening patients has been increased in the last months up to a total of 502 subjects. Moreover, the inclusion of Chinese sites in the study will contribute to enrolment. The applicant expects the enrolment to be completed by July 2021 and that the primary outcome CSR will be available by May 2023. Considering that an indication in the first line setting (i.e. in RET fusion-positive NSCLC treatment-naïve patients) is not currently pursued by the applicant, the feasibility of the study is not questioned.

Study J2G-MC-JZJB (LIBRETTO-531) is a global, multicentre, randomised (2:1), open-label, Phase 3 study comparing selpercatinib to physician's choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naive, RET-mutant MTC. As of 27 October 2020, 158 sites have been selected, of which 93 have initiated. A total of 18 patients have been enrolled so far in the study, 65 patients have consented for RET testing and 29 are on the pre-screening/screening phase. Enrolment is expected to be completed by August 2023 and the CSR is expected by September 2024. Since the indication in the first line setting (i.e. in patients with RET-mutant MTC cabozantinib/vandetanib naïve) is not further pursued by the applicant, completion of the study is considered feasible.

- Unmet medical needs will be addressed, in view of the high overall response rates and the long duration of response of selpercatinib in the applied indications. It can be assumed that there will be a clinical benefit in these patients which will be confirmed post authorisation as described above.
- 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 indications as described above, this is considered fulfilled.

3.8. Conclusions

The overall B/R of Retsevmo is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

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

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Retsevmo is favourable in the following indication:

Retsevmo as monotherapy is indicated for the treatment of adults with:

– advanced RET fusion positive non small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy

– advanced RET fusion positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

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 fusion-positive NSCLC, the MAH should submit the clinical study report of the Phase 3 study J2G-MC-JZJC (LIBRETTO-431) comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC. The CSR should be submitted by	31 October 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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that selpercatinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Appendix

1. CHMP AR on similarity dated 10 December 2020