22 April 2022
EMA/583379/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Retsevmo

International non-proprietary name: selpercatinib

Procedure No. EMEA/H/C/005375/II/0011

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

Note

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

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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

ADR adverse drug reaction

AE adverse event

AESI adverse event of special interest

ALK anaplastic lymphoma kinase

ALT alanine aminotransferase

AST aspartate aminotransferase

AUC area under the curve

AUC(0-∞) area under the plasma concentration-versus time curve from time zero to infinity

AUC0-12 area under the plasma concentration-versus time curve from time zero through 12 hours

AUC0-24 area under the concentration versus time curve, from time 0 to 24 hours

BID twice daily

CHMP Committee for Medicinal Products for Human Use

CI confidence interval

Cmax maximum observed drug concentration

CNS central nervous system

CR complete response

CSR clinical study report

CTCAE common terminology criteria for adverse events

DDI drug-drug interaction

DOR duration of response

ECG electrocardiogram

ECOG Eastern Cooperative Oncology Group

eGFR estimated glomerular filtration rate

ESMO European Society for Medical Oncology

EU European Union

GFR GDNF family receptor-α

IAS Integrated Analysis Set

INV Investigator

IRC Independent Review Committee

KRAS Kirsten rat sarcoma viral oncogene homolog

MA marketing authorisation

MAA marketing authorisation application

MedDRA Medical Dictionary for Regulatory Activities: a standard coding terminology for adverse events used globally in compliance with International Conference for Harmonisation (ICH) guidelines

MEN multiple endocrine neoplasia

MKI multikinase inhibitors

mOS median overall survival

mPFS median progression-free survival

ms millisecond

MTC medullary thyroid cancer

NA analysis not performed

NDA New Drug Application

NE not estimable

NGS next generation sequencing

NSCLC non-small cell lung cancer

NTRK Neurotrophic tropomyosin receptor kinase

ORR objective response rate

OS overall survival

PAS Primary Analysis Set

PD pharmacodynamic

PD-1 programmed cell death 1 receptor

PD-L1 programmed cell death ligand 1

PFS progression-free survival

P-gp P-glycoprotein

PK pharmacokinetic

PR partial response

PT preferred term

QTc corrected QT interval

QTcF QT interval corrected using Fridericia's Formula

RAI radioactive iodine

RECIST Response Evaluation Criteria in Solid Tumours

Response therapeutic-area-specific terms

RET rearranged during transfection

ROS1 reactive oxygen species 1

RT radiotherapy

SAE serious adverse event

SCE Summary of Clinical Efficacy

SmPC Summary of Product Characteristics

TEAE treatment-emergent adverse event

TESAE treatment-emergent serious adverse event

Tmax time to maximum plasma concentration

TTR time to response

US United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 10 November 2021 an application for a variation.

The following variation was requested:

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

Extension of indication to include the first-line treatment of RET fusion-positive NSCLC for Retsevmo based on results from study LIBRETTO-001, an open-label, multicentre, global Phase 1/2 study of selpercatinib in patients with RET-altered advanced solid tumours; as a consequence, sections 4.1, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0399/2021 on the acceptance of a modification of an agreed Paediatric Investigation Plan for selpercatinib (restevmo) (P/0369/2019). Some timelines of the PIP have been modified.

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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. However, the MAH withdrew the request during the procedure.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	10 November 2021
Start of procedure:	27 November 2021
CHMP Rapporteur Assessment Report	21 January 2022
PRAC Rapporteur Assessment Report	31 January 2022
PRAC members comments	2 February 2022
PRAC Outcome	10 February 2022
CHMP members comments	14 February 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 February 2022
Request for supplementary information (RSI)	24 February 2022
CHMP Rapporteur Assessment Report	06 April 2022
CHMP members comments	11 April 2022
Updated CHMP Rapporteur Assessment Report	13 April 2022
Opinion	22 April 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The sought extension of indication is: "Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC)".

Epidemiology

Lung cancer is the second most diagnosed cancer and the most common cause of death due to cancer with approximately 2.2 million new cases and 1.8 million deaths in 2020 (Sung H et al, 2021). Approximately 80% to 90% of lung cancers are NSCLC (Perez-Moreno et al. 2012; ESMO 2019).

Approximately 75% of lung adenocarcinomas harbour genetic alterations that promote the RTK/RAS/RAF signalling pathway including drivers such as KRAS, EGFR, ALK, ROS1, BRAF, MET, NTRK, and RET, among others (Inamura, 2017; Rosell and Karachaliou, 2016).

RET fusions are present in 1% to 2% of NSCLC patients of both Asian and European descent (Kohno et al. 2013; Ferrara et al. 2018) and the RET fusions are typically found in adenocarcinoma histology, though occasionally also in squamous cell carcinoma (Lin et al, 2015; Takeuchi et al, 2019).

Biologic features

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

Clinical presentation, diagnosis and stage/prognosis

Most patients with NSCLC present with metastatic or advanced stage, unresectable disease, and poor prognosis, with a 5-year survival rate of 6% for patients diagnosed with distant disease (ESMO 2019; ACS 2020). In addition, the symptoms associated with advanced and metastatic NSCLC represent a significant burden to patients and include dyspnea, cough, fatigue, anxiety, depression, insomnia, and pain.

Patients with RET fusion-positive lung cancer commonly have brain metastases at rates similar to the overall NSCLC population, in approximately 20% to 50% of patients (Fenske et al. 2017; Drilon et al.

2018). RET fusion-positive lung cancer is associated with identifiable clinicopathologic characteristics including younger age, never-smoker status, with relatively equal sex distribution, early lymph node metastases, and a solid predominant subtype. RET rearrangement seems to be mutually exclusive with other driver alterations (e.g., EGFR, ROS1, KRAS) (Wang et al. 2012).

For NSCLCs, including lung adenocarcinomas, no significant difference has been reported in progression - free survival (PFS) or overall survival (OS) between untreated patients with RET-positive and RET-negative tumours (Wang et al, 2012).

Management

RET fusion-positive NSCLC patients are treated with non-targeted first-line treatment options, which consist of platinum-based doublet chemotherapy, alone or in combination with an immune checkpoint inhibitor. Currently recommended subsequent therapies after progression on platinum doublet-based therapy consist generally of immune checkpoint inhibitor monotherapy, single agent chemotherapy, or docetaxel in combination with ramucirumab (Planchard et al, 2018).

Vandetanib and cabozantinib are included in the NCCN guidelines as a possible treatment option in certain circumstances (NCCN 2021) but have not received regulatory approval for the indication of RET fusion-positive NSCLC.

In 18 Nov 2021, Gavreto (Pralsetinib) a selective RET inhibitor targeting aberrant signaling resulting from oncogenic RET alterations, was approved in Europe for the treatment of advanced RET fusion-positive NSCLC based on data from a Phase I/II study (ARROW study).

2.1.2. About the product

Selpercatinib is an inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase.

RETSEVMO (Selpercatinib) was granted a CMA on 11 Feb 2021 for 1) the treatment of metastatic RET fusion-positive NSCLC in adult patients who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy, 2) RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib and 3) RET-mutant MTC in adult and pediatric patients 12 years of age and older who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

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

The presence of a RET gene fusion (NSCLC and non-medullary thyroid cancer) or mutation (MTC) should be confirmed by a validated test prior to initiation of treatment with Retsevmo.

The recommended dose of Retsevmo based on body weight is:

-Less than 50 kg: 120 mg twice daily.

-50 kg or greater: 160 mg twice daily.

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

Treatment should be continued until disease progression or unacceptable toxicity.

The MAH is seeking an extension of indication of selpercatinib for the first line treatment of advanced RET fusion-positive NSCLC.

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

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

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

Data at the DCO date of 15 June 2021 are submitted to support the use of selpercatinib for the treatment of RET fusion positive advanced NSCLC in the first line. The exploratory objectives are not presented at the DCO.

The table below summarises relevant CHMP interactions for Retsevmo for the first-line RET fusion-positive NSCLC indication.

Table 1: Selpercatinib - Key Regulatory Interactions in the EU

Date	Submission /Activity	Additional Information
25 July 2019	Scientific Advice	Clinical advice on a number of development aspects including the potential for an indication including patients with *RET* fusion-positive NSCLC who are previously untreated.
20 December 2019	Initial MAA	Applied indication: for the treatment of adults with advanced RET fusion-positive NSCLC who require systemic therapy.
16 October 2020	MAA Day 180 List of Outstanding Issues	Major Objection (MO): CHMP concern that completion of Phase 3 study could be hampered if a broad indication is given to selpercatinib for the treatment of patients with advanced *RET* fusion-positive NSCLC. Also required further justification that selpercatinib provided therapeutic advantage over existing available therapies in the sought indication.
30 October 2020	MAA Post-Day 180 Clarification Meeting	To clarify the Day 180 MO. Alignment to restrict the indication to previously treated advanced *RET* fusion-positive NSCLC.
29 June 2021	Meeting with (co)Rapporteurs and EMA	To discuss the applicant's proposal for a Type II variation to expand the indication to enable use of selpercatinib in patients with untreated *RET* fusion-positive NSCLC.

Abbreviations: CHMP = Committee for Medicinal Products for Human Use; EU = European Union; EMA = European Medicines Agency; MAA = marketing authorisation application; MO = major objection; NSCLC = non-small cell lung cancer; RET = rearranged during transfection.

2.1.4. General comments on compliance with GCP

The MAH stated that the clinical trial LOXO-RET-17001 that support the proposed indication of selpercatinib was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS), International Ethical Guidelines for Biomedical Research Involving Human Subjects, and the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guideline (E6).

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

Study LOXO-RET-17001 was subject to independent audit by regulatory authorities. The audits

performed as of 15 June 2021 were:

Table 2. Audits performed for Study LOXO-RET-17001 as of 15 June 2021

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

Abbreviations: US FDA = United States Food and Drug Administration

2.2. Non-clinical aspects

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

Environmental risk assessment

The Phase I ERA provided by the MAH contained no new data compared to the one submitted with the initial MAA. The justification from the MAH for not providing a new ERA was the following: "*The calculated prevalence in the variation is the same as that calculated in the original Phase I ERA, therefore, the concentration of selpercatinib in surface water is the same as in the original MAA and the conclusion of lack of risk to the environment is the same".*

The PEC calculated from prevalence data in Italy (showing the highest prevalence in Europe) is less than 10 ng/L. The Kow is less than 4.5. No phase II studies have been conducted. The product is considered to have a low risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study ID	Study Title and Description	Study Objectives or Outcomes	Patient, Study Participant, or Tumor Population	Number of Treated Participants
Registration Study				
LOXO-RET-7001 (J2G-OX-JZJA; LIBRETTO-001)	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. Key design features: • Multicenter • Multi-cohort • Open-label • Single arm, and • Dose escalation followed by dose expansion.	**Phase 1** ***Primary objective***: To determine • MTD and/or RP2D. ***Secondary objectives***: To assess • safety and tolerability • PK, and • ORR. **Phase 2** ***Primary objective***: To assess • ORR by IRC. ***Secondary objectives***: To assess • ORR by IA • DOR, TTBR, PFS, CBR, best change in tumor size by IRC and IA • CNS ORR and DOR by IRC • OS • safety and tolerability, and • PK.	*RET* fusion-positive NSCLC	356
			RET-mutant MTC	319
			RET fusion-positive thyroid cancer	54
			RET fusion-positive other cancers	43
			Other cancers	24
			Total[a]	796
J2G-MC-JZJV	An Open-Label Study to Investigate the Effect of Selpercatinib on the Pharmacokinetics of Dabigatran in Healthy Volunteers. Key design features: • Open-label, and • Single center.	***Primary objectives:*** Evaluate the effect of selpercatinib on P-gp activity, assessed by C_{max} and AUC(0-∞). ***Secondary objectives:*** Evaluate the effect of dabigatran in combination with selpercatinib on • safety and tolerability, and • PK parameters: C_{max}, t_{max}, and $AUC_{(0-\infty)}$.	Healthy participants	36

Abbreviations: $AUC_{(0-\infty)}$ = area under the concentration versus time curve, from the time of dosing to infinity; C_{max} = maximum observed plasma concentration; CBR = clinical benefit rate; CNS = central nervous system; CSR = clinical study report; DOR = duration of response; IA = investigator assessment; IRC = Independent Review Committee; LOXO-292 = selpercatinib; MTC = medullary thyroid cancer; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; P-gp = P-glycoprotein; PK = pharmacokinetics; *RET* = rearranged during transfection; RP2D = recommended Phase 2 dose; t_{max} = time to maximum observed concentration; TTBR = time-to-best response.

[a] Patients treated in LIBRETTO-001 as of 15 June 2021 data cutoff.

Sources: LIBRETTO-001 Interim CSR Addendum (15 June 2021 data cutoff) and J2G-MC-JZJV CSR.

2.3.2. Pharmacokinetics

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

In Europe, selpercatinib is approved under the brand name of Retsevmo®. Two strengths of hard capsules, 40 and 80 mg are available. Selpercatinib is actually used as monotherapy 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

Selpercatinib is also indicated as monotherapy 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.

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

- Less than 50 kg: 120 mg twice daily.

- 50 kg or greater: 160 mg twice daily.

The pharmacokinetic (PK) properties of selpercatinib were sufficiently characterized in the initial MAA and are summarized below as described in the actual adopted SmpC.

In the current submission, the applicant seeks a modification of the indication of selpercatinib to include the treatment of RET fusion-positive NSCLC in the first-line setting (treatment of RET fusion-positive advanced NSCLC regardless of line of therapy).

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

The PK data provided in support of this submission includes:

- Descriptive, noncompartmental methods of analysis of selpercatinib PK data from all patients enrolled in the pivotal study LOXO-RET-17001 (LIBRETTO-001) as of the submission data cut-off date (15 June 2021) for whom PK data were not previously reported in the initial MAA.

The additional PK data from the pivotal study LOXO-RET-17001 are presented in the paragraph "PK in target population".

Absorption

After an oral dose of 160 mg, Retsevmo was rapidly absorbed, with Tmax of approximately 2 hours. Geometric mean absolute oral bioavailability was 73.2% (range: 60.2-81.5%).

Effect of food

Compared to selpercatinib AUC and Cmax in the fasted state, selpercatinib AUC was increased by 9% and Cmax was reduced by 14% after oral administration of a single 160 mg dose to healthy subjects taken with a high-fat meal. These changes were not considered to be clinically relevant. Therefore, selpercatinib can be taken with or without food.

Distribution

Selpercatinib mean (CV%) volume of distribution (Vss/F), estimated by Population PK analysis, is 191 (69%) L following oral administration of selpercatinib in adult patients. Selpercatinib is 96% bound to human plasma proteins in vitro and binding is independent of concentration. The blood-to-plasma concentration ratio is 0.7.

Elimination

The mean (CV%) clearance (CL/F) of selpercatinib is 6.0 (49%) L/h and the half-life is 22 hours following oral administration of selpercatinib in adult patients. Following oral administration of a single [14C] radiolabeled 160 mg dose of selpercatinib to healthy subjects, 69% (14% unchanged) of the administered radioactivity was recovered in faeces and 24% (11.5% unchanged) was recovered in urine.

Dose proportionality and time dependencies

The pharmacokinetics of selpercatinib were evaluated in patients with locally advanced or metastatic solid tumors administered 160 mg twice daily unless otherwise specified. Steady-state selpercatinib AUC

and Cmax increased in a linear to supra-dose proportional manner over the dose range of 20 mg once daily to 240 mg twice daily.

Steady-state was reached by approximately 7 days and the median accumulation ratio after administration of 160 mg twice daily was 3.4-fold. Mean steady-state selpercatinib [coefficient of variation (CV%)] Cmax was 2,980 (53%) ng/mL and AUC0-24h was 51,600 (58%) ng*h/mL.

Special populations

Age, gender and body weight

Age (range: 15 years to 90 years) or gender had no clinically meaningful effect on the pharmacokinetics of Retsevmo. Patients with a body weight ≤50 kg should start Retsevmo treatment with a dose of 120 mg twice daily, while patients >50 kg should start Retsevmo treatment with a dose of 160 mg twice daily.

Hepatic impairment

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). There is limited clinical data on the safety of selpercatinib in patients with severe hepatic impairment. Therefore, dose modification is recommended for patients with severe hepatic impairment (section 4.2).

Renal impairment

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

Paediatric population

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

Pharmacokinetics in target population

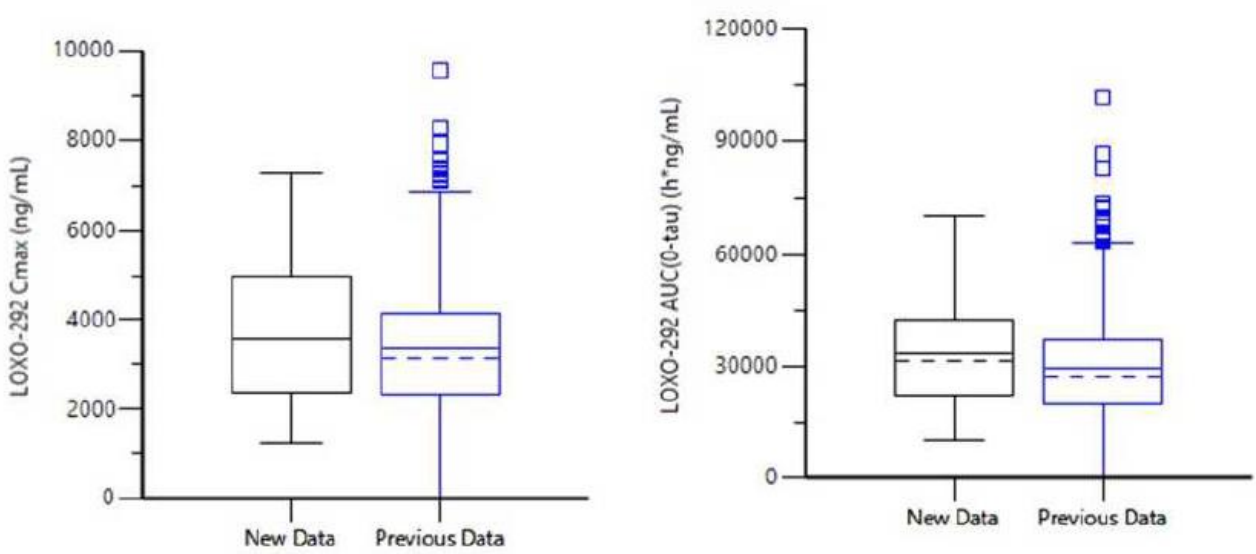
Table 3 summarizes the steady-state PK parameters (Cycle 1 Day 8) for plasma selpercatinib concentrations in patients receiving 160 mg BID dose in the pivotal study LIBRETTO-001 collected from 09 May 2017 to 30 March 2020 (previous data submitted in the initial MAA) and from 01 April 2020 to 10 June 2021 (new data), respectively. A comparsion of steady-state AUCtau between the two periods is shown in Figure 1.

Table 3 .Steady-State (Cycle 1 Day 8) Pharmacokinetic Parameters of Selpercatinib in Patients with Cancer

Actual Dose	Data Period		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)	CL_{ss}/F (L/h)
160 mg BID	09 May 2017 to 30 March 2020	N	614	614	614	601	601	601
		GM	2.00	3050	26100	26300	52600	6.08
		GCV%	0.00-8.10	51.4	55.7	55.5	55.5	55.5
	01 April 2020 to 10 June 2021	N	32	32	32	30	30	30
		GM	2.15	3310	29700	30200	60300	5.31
		GCV%	0.00-8.08	44.5	47.4	47.7	47.7	47.7

AUC0-24 = area under the plasma concentration-time curve from time 0 to 24 hours; AUC0-last = area under the plasma concentration-time curve up from time zero to the last observable concentration; AUC0-tau (AUC0-12) = area under the plasma concentration-time curve from time 0 to 12 hours; BID = twice daily; CLss/F = apparent total clearance of drug after oral administration at steady state; Cmax = maximum plasma concentration; CV% = percent coefficient of variation; GCV% = geometric CV%; GM = geometric mean; max = maximum; min = minimum; N = number of samples; Tmax = time to reach maximum plasma concentration.

Figure 1: Boxplots of plasma selpercatinib Cmax and AUC0-tau following selpercatinib 160 mg BID administrations of capsule formulation (Cycle 1 Day 8)



The dashed line is the median; the solid line is the arithmetic mean. The ends of the "box" are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile and the highest value still within 1.5 IQR of the upper quartile, where IQR is the interquartile range (the difference between the third and first quartiles, the middle 50%).

The steady-state PK parameters (Tmax, Cmax, and AUC0-24) for patients with evaluable data at Cycle 1 Day 8 were previously calculated by non-compartmental analyses. The NCA PK parameters for patients with NSCLC from data cuts of 09 May 2017 to 30 March 2020 (LOXONCA- LOXO292-1229) and 01 April 2020 to 10 June 2021(LOXO-NCA-LOXO292-2829) were combined with tumour type data and treatment status for the analysis:

- geometric means and coefficient of variation summary statistics are provided in Table 4, and

- bar charts showing the mean and 90% percentile intervals are provided in Figure 2.

Table 4. Steady-State (Cycle 1 Day 8) Pharmacokinetic Parameters of Selpercatinib in Patients with NSCLC

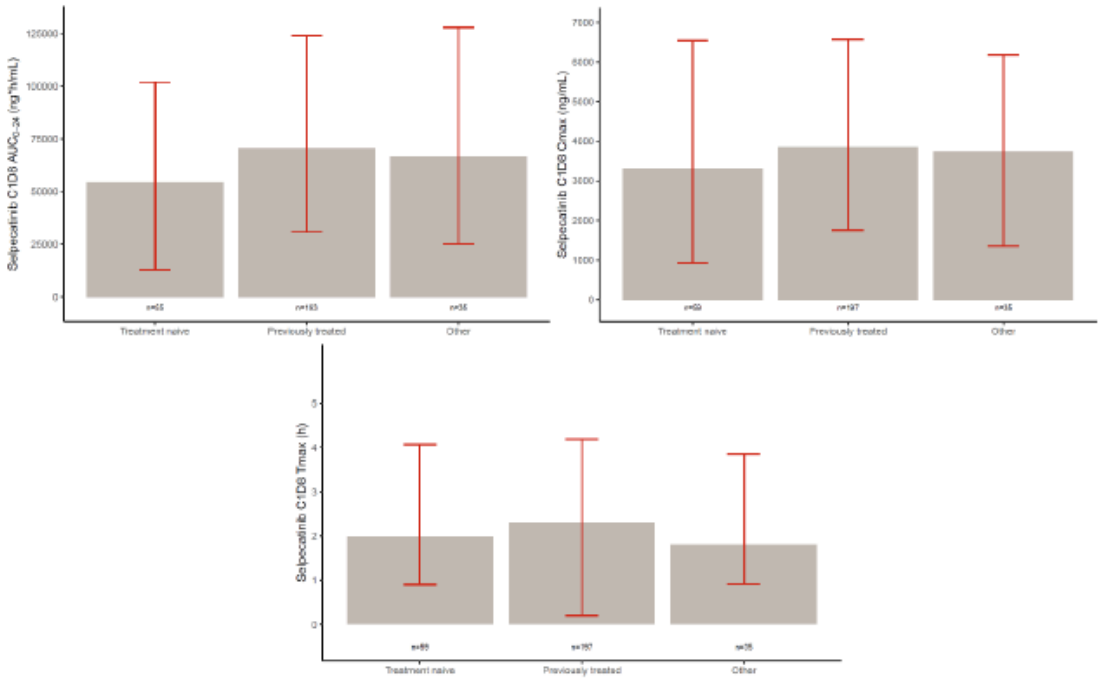
	Treatment-Naïve Patients			Patients Previously-Treated with Platinum-Based Chemotherapy			Patients Previously-Treated with Other Therapies		
	T_{max}[a] (h)	C_{max} (ng/mL)	AUC_{0-24} (h·ng/mL)	T_{max}[a] (h)	C_{max} (ng/mL)	AUC_{0-24} (h·ng/mL)	T_{max}[a] (h)	C_{max} (ng/mL)	AUC_{0-24} (h·ng/mL)
N	59	59	55	197	197	193	35	35	35
GM	2.0	2930	46700	2.0	3570	64800	2.0	3380	60100
GCV%	0.8 - 4.3	58	67	0 - 8.1	42	45	0 - 4.0	54	53

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours; C_{max} = maximum plasma concentration; GCV% = geometric coefficient of variation; GM = geometric mean; N = number of samples; NSCLC = non-small cell lung cancer; T_{max} = time of maximum concentration.

a Median and range (minimum – maximum).

Data available from 09 May 2017 to 10 June 2021.

Figure 2. Bar charts of plasma selpercatinib Tmax, Cmax, and AUC0-24 following selpercatinib 160 mg BID administrations (Cycle 1 Day 8) in treatment-naïve patients, patients previously-treated with platinum-based chemotherapy, and patients previously-treated with other therapies.



Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours; BID = twice daily; C1D8 = Cycle 1 Day 8; C_{max} = maximum plasma concentration; n = number of patients in the specified category; T_{max} = time of maximum plasma concentration.

"Previously treated" refers to patients previously treated with platinum-based chemotherapy.

"Other" refers to patients previously treated with other therapies (see Table 3.1).

The bar height is the mean. The whiskers show the 5th and 95th percentiles of the data. The numbers below each box plots refer to the number of patients.

Data cut-off date 10 June 2021.

2.3.3. Pharmacodynamics

Mechanism of action

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

Primary and secondary pharmacology

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

2.3.4. PK/PD modelling

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

2.3.5. Discussion on clinical pharmacology

No complementary formal PK investigations have been carried out in the context of the variation under review. Additional new PK data from the pivotal study LOXO-RET-17001 (n=32, collected from 01 April 2020 to 10 June 2021) have been provided and compared to the previous data already submitted in the initial MAA (n= 614, collected from 09 May 2017 to 30 March 2020). Furthermore, a comparison of steady-state selpercatinib PK parameters in the target NSCLC patients treatment-naïve using the recommended 160 mg BID dose with the reference NSCLC patients who had prior therapy is provided.

Overall, the PKs of selpercatinib in the target patients was assessed and the updated data identified no significant difference compared to other /current NSCLC cancer patients.

2.3.6. Conclusions on clinical pharmacology

The applicant applied for an extension of the indication to include adult patients with RET fusion-positive NSCLC in the first-line setting (treatment-naïve) in addition to patients with RET fusion-positive non-small cell lung cancer NSCLC who had prior therapy (currently approved). Overall, no significant difference in PKs characteristics of selpercatinib is observed in the target patients by comparison to other cancer patients already assessed in the already authorised indication. No revision of section 5.2 of the SmpC is required.

2.4. Clinical efficacy

2.4.1. Dose response study

Study LIBRETTO-001 is an open-label, multicentre, global Phase 1/2 study of selpercatinib in patients with RET-altered advanced solid tumours that was initiated in May 2017. The Phase 1 portion of the

study allowed to determine the maximum tolerated dose and recommended Phase 2 dose of selpercatinib. A dose of 160 mg BID was selected for Phase 2.

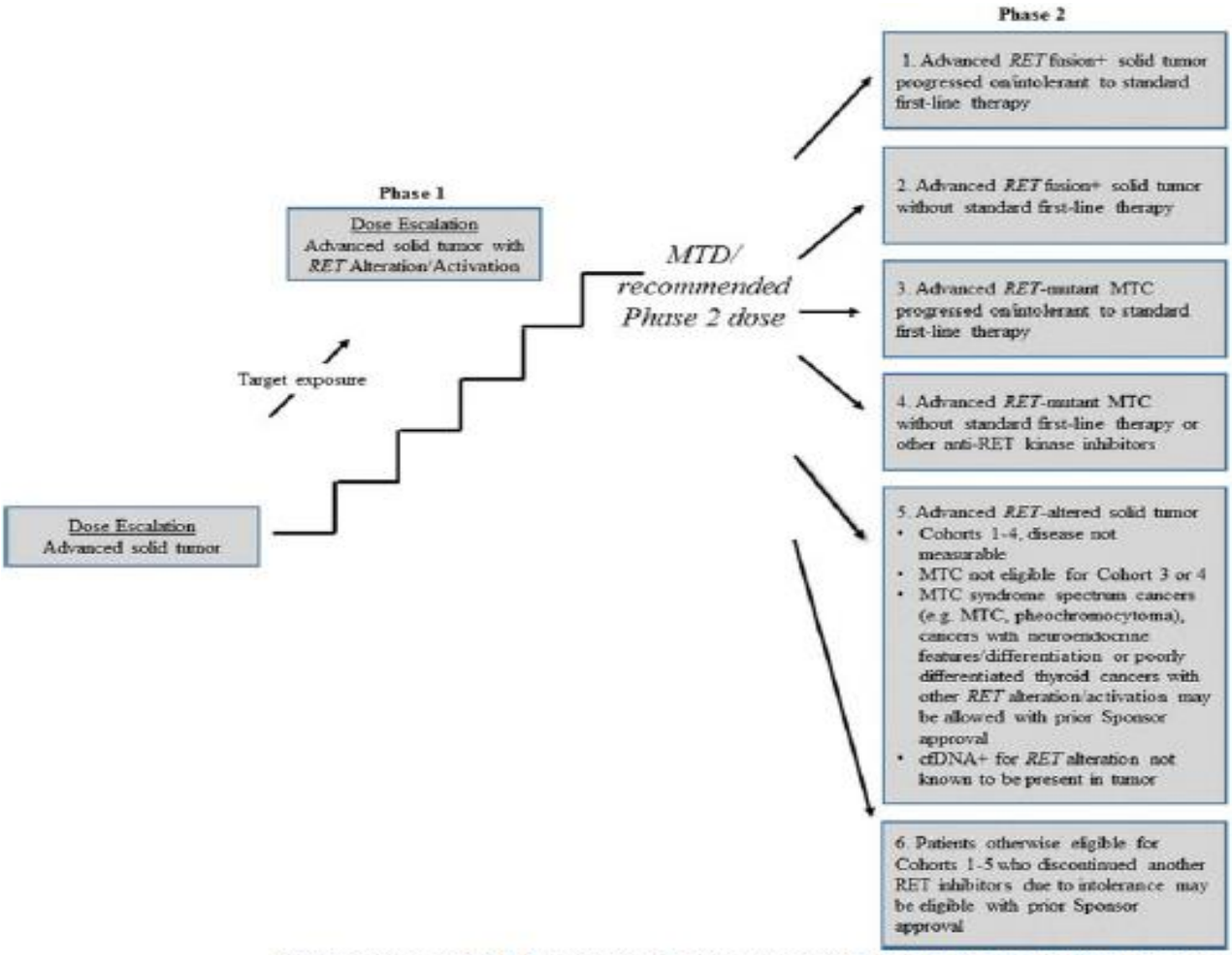
The approved dose as recommended in the SmPC is 160 mg taken orally twice daily (body weight 50 mg or greater).

2.4.2. Main study

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

Methods

Figure 3: depicts the study design for the protocol version 9.0.



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

Study participants

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

Inclusion Criteria for Phase 1

- Inclusion Criterion [2] – amended to remove the prohibition of prior treatment with a selective RET inhibitor(s) (including investigational selective RET inhibitor[s]).
- Inclusion Criterion [5] - amended to note the exclusion of minor patients in Canada and Germany.
- Criterion [11]: - allowed enrolment of patients with adequate renal function, with estimated glomerular filtration rate ≥ 30 mL/minute (up to 6 participants with an eGFR ≥ 15 and < 30 mL/minute were allowed to enroll with Sponsor approval).
- Criterion [13]: - amended to include additional details on observing conventional and effective birth control for the duration of treatment and for 3 months

Inclusion Criteria for Phase 2

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

Exclusion Criteria for Phase 1 and Phase 2:

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

Treatments

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

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

Objectives/Endpoints

Table 5. Objectives and endpoints of LIBRETTO-001 (Phase 2)

Objectives (Phase 2)	Endpoints (Phase 2)
Primary	
• To assess, for each Phase 2 expansion cohort, the anti-tumor activity of selpercatinib by determining ORR using RECIST 1.1 or RANO, as appropriate to tumor type, as assessed by IRC	• ORR based on RECIST 1.1 or RANO, as appropriate to tumor type, as assessed by IRC
Secondary	

• To assess, for each expansion cohort, the anti-tumor activity of selpercatinib by determining:
  • ORR based on RECIST 1.1 or RANO, as appropriate to tumor type, as assessed by Investigator
  • Best change in tumor size from baseline, as assessed by IRC and Investigator
  • DOR as assessed by IRC and Investigator
  • CNS ORR based on RECIST 1.1 or RANO, as appropriate to tumor type, as assessed by IRC (for participants with brain metastases)
  • CNS DOR as assessed by IRC (for participants with brain metastases)
  • Time to any and best response based on RECIST 1.1 or RANO, as appropriate to tumor type, as assessed by IRC and Investigator
  • CBR based on the proportion of participants with best overall response of CR, PR, or SD lasting 16 or more weeks following initiation of selpercatinib, as assessed by IRC and Investigator
  • PFS as assessed by IRC and Investigator
  • OS following initiation of selpercatinib
	• Parameters of anti-tumor activity/clinical benefit, including:
	  • ORR (by Investigator)
	  • Best change in tumor size from baseline (by IRC and Investigator)
	  • DOR (by IRC and Investigator)
	  • CNS ORR (by IRC)
	  • CNS DOR (by IRC)
	  • Time to any and best response (by IRC and Investigator)
	  • CBR (by IRC and Investigator)
	  • PFS (by IRC and Investigator)
	  • OS

• To determine the safety profile and tolerability of selpercatinib	• Frequency, severity, and relatedness of TEAEs and SAEs • Changes in hematology and blood chemistry values • Assessments of physical examinations • Vital signs • ECGs
• To characterize the PK properties of selpercatinib	• Plasma concentrations of selpercatinib and PK parameters, including, but not limited to, AUC_{0-24}, C_{max}, and T_{max}[a]

Abbreviations: AUC_{0-24} = area under the concentration versus time curve from time 0 to 24 hours; CBR = clinical benefit rate; C_{max} = maximum drug concentration; CNS = central nervous system; CR = complete response; DOR = duration of response; ECG = electrocardiogram; IRC = Independent Review Committee; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; RANO = Response Assessment in Neuro-Oncology Criteria; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease; TEAE = treatment-emergent adverse event; T_{max} = time to maximum plasma concentration.

[a] PK data will be analyzed and presented in this interim report for those patients whose PK data were not previously reported.

Sample size

Phase 2

For Cohort 1 (patients with RET fusion-positive solid tumours who have progressed on or are intolerant to standard first-line therapy for their cancers), a sample size of 55 patients is 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%.

For Cohort 2 (patients with RET fusion-positive solid tumours without prior standard first-line therapy), a sample size of 59 patients is 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 have progressed on or are intolerant to vandetanib and/or cabozantinib), a sample size of 83 patients is 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%.

For Cohort 4 (patients with RET-mutant MTC who are MKI-naïve), a sample size of 55 patients is 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%.

Enrolment beyond the above sample sizes in each of Cohorts 1-5, will be allowed, in order to accommodate enrollment demand and allow for the characterization 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% is 77.9% and 95.2%, respectively. The sample size for Cohort 1 was increased to ~250 to accommodate enrollment demand. Additional enrollment will also allow for the characterization of AEs that may occur with low frequency which would enhance knowledge of the safety profile of selpercatinib. Further, this cohort allows for the enrollment of patients with RET fusion-positive solid tumours other than NSCLC. While the enrollment demand for patients with RET fusion-positive NSCLC has been adequate for statistical analysis, additional solid tumour types remain underrepresented and enrollment expansion allows for data capture in this population.

Up to ~50 patients will be enrolled into Cohort 6 based on clinical consideration. Exploring efficacy in patients with a history of prior exposure to RET specific inhibitors may enhance understanding of the risk:benefit of additional RET specific therapy in these patients and aid in the consideration of resistance mechanisms in response to this type of therapy.

Randomisation and blinding (masking)

The study is non-randomized and non-blinded single arm study.

Statistical methods

There were no changes in the planned analyses for the study except some with minimal impact which are described in the SAP addendum dated 14 June 2021.

The overall rationale for the RET fusion-positive NSCLC SAP Addendum 1 is to outline the FDA RET fusion-positive NSCLC Accelerated Approval Requirement (AAR) and detail considerations for the sNDA submission cutoff date.

In addition, subgroup analyses are planned for patients with vs without prior immune checkpoint inhibitor (ICI) therapy.

Intracranial Analysis

Time to CNS progression will be explored. Time to CNS progression is defined as the time from randomization until the occurrence of documented CNS progression by the IRC.

CNS progression, non-CNS progression, and death are competing risk events; CNS progression is the event of interest defined as progression due to newly developed intracranial lesions and/or progression of pre-existing intracranial lesions per RECIST version 1.1.

To account for the competing risks, the probability of the first event of CNS progression, non- CNS progression, or death without any progression will be estimated using a cumulative incidence function (sub-distribution function). A plot of the estimated cumulative-incidence functions will be displayed.

Intra-patient Analysis

Prior therapy data will be used to perform an exploratory analysis comparing benefit achieved on the last therapy patients received prior to the study enrollment to benefit achieved on selpercatinib treatment using each study patient as their own control. A known limitation of this analysis is retrospective prior therapy data collection based on patients' medical records without central review and confirmation based on RECIST criteria.

There is no change to efficacy analysis sets defined in the original version of the NSCLC SCE SAP.

Patients enrolled into the Phase 1 dose escalation as well as the Phase 1 and Phase 2 dose expansion cohorts were grouped to derive the analysis sets. The goal of the arrangement of these various data sets was to:

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

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

Patients with RET fusion-positive NSCLC who had received at least 1 dose of selpercatinib and achieved at least 6 months of potential follow-up time from the first dose of selpercatinib (or disease progression or death, whichever occurred first), as of 15 June 2021, were considered eligible for efficacy analyses.

The evaluation of efficacy consists of RET fusion-positive NSCLC analysis sets as defined in Table 3.2 (the basis for the initial regulatory submissions) and includes patients enrolled into Cohorts 1, 2, and 5. Cohort 6 includes patients who have received prior treatment with a selective RET inhibitor and are therefore not included in the efficacy analysis; these patients were excluded in LIBRETTO-001 until Cohort 6 was introduced in Protocol version 8.

The efficacy analysis for RET fusion-positive NSCLC primarily focused on 1) previously treated patients and 2) treatment-naïve patients. Efficacy was further assessed using the supportive efficacy analysis sets described in Table 3.2, including a CNS Response Analysis Set consisting of all patients with RET fusion-positive NSCLC who have investigator-identified CNS metastases at baseline (reported as target or nontarget lesion per RECIST v1.1).

Table 6: Description of Efficacy Analysis Sets

Efficacy Analysis	Analysis Set	Analysis Set Description
Primary efficacy analysis set	**Treatment-Naïve Patients (N=69)** (previously named SAS1)	Includes treatment-naïve patients with *RET* fusion-positive NSCLC who met Criteria 1, 2, and 4 in footnote "a". **These data support the proposed indication in the first-line setting.**
Supportive efficacy analysis sets	**Patients Previously Treated with Platinum-Based Chemotherapy (N=247)** (previously named IAS)	Includes all patients with *RET* fusion-positive NSCLC previously treated with platinum-based chemotherapy who met the criteria in footnote "a".
	Patients Previously Treated with Other Systemic Therapy (N=19) (previously named SAS2)	Includes patients with *RET* fusion-positive NSCLC previously treated with systemic therapies other than platinum-based chemotherapy who met Criteria 1, 2, and 4 in footnote "a".
	Patients with Non-Measurable Disease (N=20) (previously named SAS3)	Includes previously treated and treatment naïve patients with *RET* fusion-positive NSCLC without measurable disease by RECIST 1.1 and met Criteria 1 and 4 in footnote "a".
	The First 105 Patients Enrolled who were Previously Treated with Platinum-Based Chemotherapy (N=105) (previously named PAS)	Includes the first 105 consecutively enrolled patients with *RET* fusion-positive NSCLC previously treated with platinum-based chemotherapy who met the criteria in footnote "a". This analysis set is a subset of the "Patients Previously Treated with Platinum-Based Chemotherapy" analysis set and was presented in the SmPC but is being superseded by the data presented in this submission dossier.
	CNS Response Analysis Set[b] (N=106)	Includes patients with *RET* fusion-positive NSCLC who had investigator-identified CNS metastases at baseline (reported as target or nontarget lesion per RECIST 1.1). This analysis set contains patients from across the primary and supportive efficacy analysis sets.

Abbreviations: CLIA = Clinical Laboratory Improvement Amendment; CNS = central nervous system; IAS = Integrated Analysis Set; NSCLC = non-small cell lung cancer; PAS = Primary Analysis Set; RECIST = Response Evaluation Criteria in Solid Tumors; SAP = statistical analysis plan; SAS = Safety Analysis Set; SCE = summary of clinical efficacy.

[a] Criteria for inclusion:

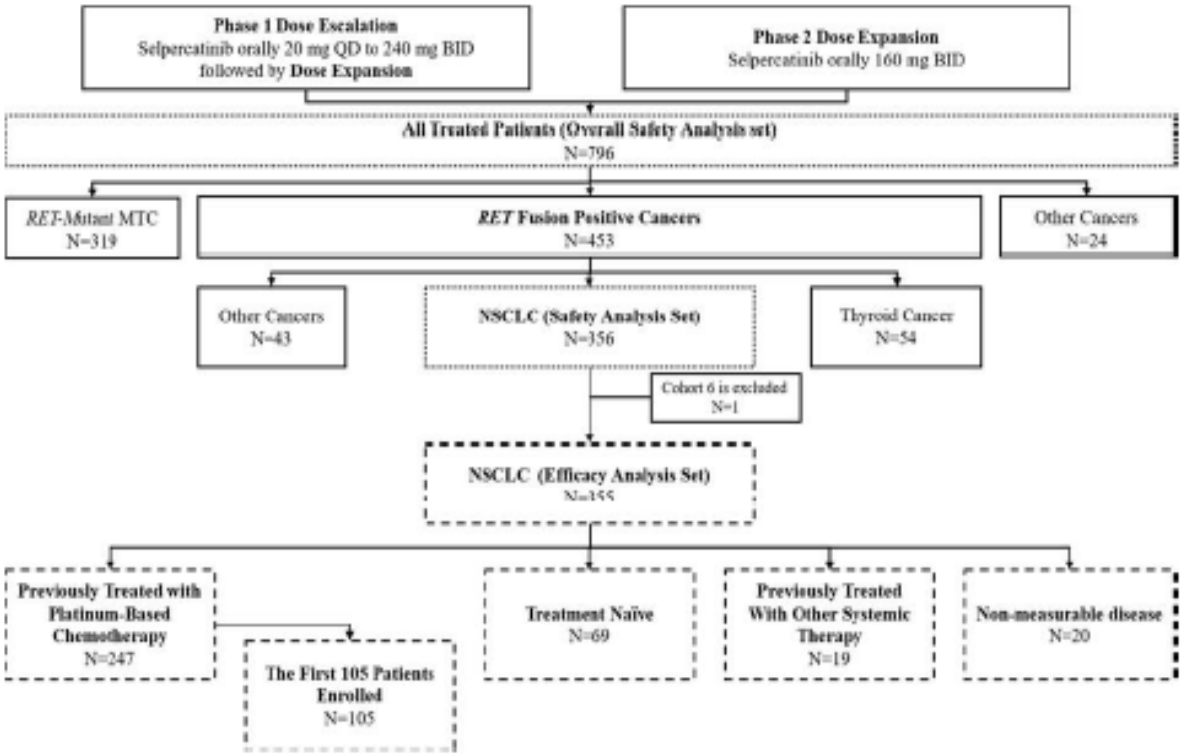
1. Evidence of a protocol-defined qualifying and definitive *RET*-fusion, prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) Molecular Pathology Report. Patients with a *RET* fusion co-occurring with another putative oncogenic driver, as determined at the time of study enrolment by local testing, were included.
2. Measurable disease by RECIST 1.1 by investigator assessment. Patients without measurable disease who were enrolled in Phase 1 dose escalation were included in the "Patients Previously Treated with Platinum-Based Chemotherapy" and "The First 105 Patients Enrolled who were Previously Treated with Platinum-Based Chemotherapy" Analysis Sets. Refer to the NSCLC SCE SAP for details.
3. Received 1 or more lines of prior platinum-based chemotherapy.
4. Received 1 or more doses of selpercatinib.

[b] This analysis set provides evidence for selpercatinib's activity in patients with *RET* fusion-positive NSCLC and CNS metastases (N=106). Of these 106 patients, 26 had measurable disease and 80 had non-measurable disease at baseline as assessed by the investigator.

Results

Participant flow

Figure 4: RET fusion-positive NSCLC efficacy analysis and overall safety populations based on a data cutoff date of 15 June 2021 LIBRETTO-001.



Abbreviations: BID = twice daily; MTC = medullary thyroid cancer; N = number of patients; NSCLC = non-small cell lung cancer; QD = once daily; RET = REarranged during Transfection.

Table 7. Screen Failures – Overall Safety Population (Data Cut-off: 15 June 2021)

Characteristic	Total
Subjects Screened (n)	921
Subjects Treated (n, %)*	796 (86.4)
Subjects Screened and Not Treated (n, %)*	2 (0.2)
Subjects with Screen Failure (n, %)*	123 (13.4)
Reason for Screen Failure (n, %)**	
DID NOT SATISFY ALL INCLUSION OR EXCLUSION CRITERIA	87 (70.7)
WITHDRAWAL OF CONSENT	11 (8.9)
ADVERSE EVENT	10 (8.1)
DEATH	2 (1.6)
INVESTIGATOR DECISION	2 (1.6)
OTHER	11 (8.9)

*Percentages are based on the number of subjects (n) that were screened.
**Percentages are based on the number of subjects (n) that had screen failure.

Table 8: Summary of Disposition RET Fusion-Positive NSCLC Efficacy Analysis Population (Data Cutoff: 15 June 2021)

	Primary Analysis Sets		Supportive Analysis Sets[a]		
Analysis Set	**Prior Platinum Chemotherapy**	**Treatment-Naïve**	**Prior Other Systemic Therapy**	**Non-Measurable Disease**	**Total NSCLC[b]**
Treated	247	69	19	20	355
Treatment continuing, n (%)	117 (47.4)	32 (46.4)	6 (31.6)	10 (50.0)	165 (46.5)
Continuing post progression[c]	26 (10.5)	5 (7.2)	2 (10.5)	3 (15.0)	36 (10.1)
Treatment discontinued, n (%)	130 (52.6)	37 (53.6)	13 (68.4)	10 (50.0)	190 (53.5)
Disease progression	73 (29.6)	26 (37.7)	10 (52.6)	6 (30.0)	115 (32.4)
Adverse event	23 (9.3)	6 (8.7)	0 (0.0)	3 (15.0)	32 (9.0)
Intercurrent illness compromising ability to fulfill protocol requirements	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Requirement for alternative treatment per investigator	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Withdrawal of consent	14 (5.7)	3 (4.3)	0 (0.0)	0 (0.0)	17 (4.8)
Death	8 (3.2)	2 (2.9)	3 (15.8)	1 (5.0)	14 (3.9)
Other	9 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	9 (2.5)
Treatment continued post-progression, n (%)	86 (34.8)	22 (31.9)	7 (36.8)	5 (25.0)	120 (33.8)
Study status continuing, n (%)	143 (57.9)	44 (63.8)	10 (52.6)	11 (55.0)	208 (58.6)
Study status discontinued, n (%)	104 (42.1)	25 (36.2)	9 (47.4)	9 (45.0)	147 (41.4)
Withdrawal of consent	25 (10.1)	5 (7.2)	1 (5.3)	3 (15.0)	34 (9.6)
Lost to follow-up	1 (0.4)	0 (0.0)	1 (5.3)	0 (0.0)	2 (0.6)
Death	78 (31.6)	20 (29.0)	7 (36.8)	6 (30.0)	111 (31.3)

Abbreviations: n = number of patients in specific category; NSCLC = non-small cell lung cancer; RET = REarranged during Transfection.

a Patient disposition for The First 105 Patients with Prior Platinum Chemotherapy Analysis Set is presented in Table 8.4.

b The total column is calculated from the Prior Platinum Chemotherapy, Treatment-Naïve, Prior Other Systemic Therapy, and Non-Measurable Disease Analysis Sets.

c Status as of the data cutoff date.

Recruitment

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

Study initiation date: 09 May 2017

Data cutoff date for interim analysis: 15 June 2021

Participants screened: 921

Participants treated: 796

Participants continuing study intervention: 462

Conduct of the study

This interim report provides information on study conduct from Protocol version 8.0 up to Protocol version 9.0 (03 June 2020).

Table 9: Summary of major changes, subsequent amendments, and the approval dates of the protocol.

Version Number and Date	Major Changes to the Protocol
8.0 10 June 2019	• New sections were added to define length of study and end of study • The LTFU plan was updated to occur approximately every 3 months until the participant has withdrawn consent, is lost to follow-up, has died, or the sponsor makes a decision to close the study. • Phase 2 descriptions were updated to increase participant numbers following the selection of 160 mg BID as the RP2D and to account for addition of a new cohort (Cohort 6). • Eligibility criteria were added, removed, or modified (as detailed in protocol Section 3.3.1). • Additional details were provided regarding the study intervention (protocol Section 3.4.1). • Additional Investigator guidance regarding possible AEs and re-escalations were provided. • Tests and evaluations were updated to add tests at additional time points and increase frequency of tests (as described in Section 7 of the protocol [appendix Protocol and addenda]). • Sample size was updated to reflect updated size for Cohort 1 and Cohort 6. • Statistical portions were updated to align with other protocol sections. • Clarification that efficacy analyses will be conducted on the Safety Analysis Set unless otherwise specified (as described in protocol Section 3.7). • Definition of life-threatening AEs was updated. Examples of multiple kinase inhibitors and RET activating mutations were updated.

8.1 (Denmark) 10 June 2019	Major changes from protocol version 7.3 (Denmark) to version 8.1 were: • Rationale for enrolling participants younger than 18 years was provided to indicate that participants younger than 18 years could be enrolled if approved by local institutional and country regulatory authorities. • All other revisions were made to align with version 8.0.
8.2 (Japan) 14 June 2019	Major changes from protocol version 7.2 (Japan) to version 8.2 were: • Study design was updated to add clarification of enrollment in Japan. • All other revisions were made to align with version 8.0.
8.3 (Germany) 08 October 2019	Major changes from protocol version 7.4 (Germany) to version 8.3 were: • Clinical safety and data updates were made to align with IB version 5.0. • Size of Cohort 1 was increased to up to approximately 200 participants. • Cohort 6 was added for participants who discontinued another RET inhibitor due to intolerance (up to approximately 50 participants). • The 40 mg capsule and liquid suspension were added; the 10 mg capsule was removed. • The ECG schedule was updated.
Addendum 1 to V8.0-8.3 02 April 2020	The purpose of this addendum was to allow temporary flexibility in study visits, assessments, and study drug dispensation because of the COVID-19 pandemic. The information in this addendum supplements Protocol Section 7 and Table 7-1 in Protocol version 8.0, version 8.1, version 8.2, and version 8.3.
9.0 (Global) 03 June 2020	Major changes from protocol version 8.3 (Germany) to version 9.0 were: • Aligned changes added in response to EC/RA queries in PA8.1 (Denmark), PA8.3 (Germany), and PA8 addendum (Canada). • Clinical safety and data updates were made to align with the IB V7.0. • Size of Cohort 1 was increased to approximately 250 participants and Cohort 5 up to approximately 200. • Reduced the requirement for in-clinic visits beyond C7 and provided the options of telemedicine and visits to local healthcare providers during nondisease assessment cycles.

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

Protocol Deviations

Table 10: Summary of Important Protocol Deviations (Data Cutoff: 15 June 2021)

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

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

Baseline data

Demographics

Table 11: Summary of Demographics RET Fusion-Positive NSCLC Efficacy Analysis Population (Data Cutoff: 15 June 2021)

Analysis Set	Prior Platinum Chemotherapy (N=247)	Treatment-Naïve (N=69)	Supportive Analysis Sets[a]		Total[b] (N=355)
			Prior Other Systemic Therapy (N=19)	Non-Measurable Disease (N=20)	
Age (years), n					
Median (Range)	61.0 (23-81)	63.0 (23-92)	58.0 (47-71)	56.0 (26-80)	61.0 (23-92)
Overall age group, n (%)					
18-44 years	33 (13.4)	7 (10.1)	0 (0.0)	4 (20.0)	44 (12.4)
45-64 years	127 (51.4)	31 (44.9)	14 (73.7)	10 (50.0)	182 (51.3)
65-74 years	70 (28.3)	24 (34.8)	5 (26.3)	5 (25.0)	104 (29.3)
75-84 years	17 (6.9)	4 (5.8)	0 (0.0)	1 (5.0)	22 (6.2)
≥85 years	0 (0.0)	3 (4.3)	0 (0.0)	0 (0.0)	3 (0.8)
Sex, n (%)					
Male	107 (43.3)	26 (37.7)	8 (42.1)	11 (55.0)	152 (42.8)
Female	140 (56.7)	43 (62.3)	11 (57.9)	9 (45.0)	203 (57.2)
Race, n (%)					
White	108 (43.7)	48 (69.6)	12 (63.2)	6 (30.0)	174 (49.0)
Black or African American	12 (4.9)	4 (5.8)	0 (0.0)	0 (0.0)	16 (4.5)
American Indian or Alaska Native	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	118 (47.8)	13 (18.8)	7 (36.8)	14 (70.0)	152 (42.8)
Other/Missing	8 (3.2)	4 (5.8)	0 (0.0)	0 (0.0)	12 (3.4)
Ethnicity, n (%)					
Hispanic or Latino	7 (2.8)	1 (1.4)	1 (5.3)	1 (5.0)	10 (2.8)
Not Hispanic or Latino	235 (95.1)	67 (97.1)	18 (94.7)	19 (95.0)	339 (95.5)
Missing	5 (2.0)	1 (1.4)	0 (0.0)	0 (0.0)	6 (1.7)
Body weight (kg)					
n	246	69	19	20	354
Median	64.950	71.200	59.500	62.550	64.950
Range	38.85-148.00	44.00-130.50	48.60-109.50	46.10-106.80	38.85-148.00
Baseline ECOG, n (%)					
0	90 (36.4)	25 (36.2)	5 (26.3)	11 (55.0)	131 (36.9)
1	150 (60.7)	40 (58.0)	13 (68.4)	9 (45.0)	212 (59.7)
2	7 (2.8)	4 (5.8)	1 (5.3)	0	12 (3.4)
Smoking history, n (%)					
Never smoked	165 (66.8)	48 (69.6)	13 (68.4)	15 (75.0)	241 (67.9)
Former smoker	78 (31.6)	19 (27.5)	6 (31.6)	5 (25.0)	108 (30.4)
Current smoker	4 (1.6)	2 (2.9)	0	0	6 (1.7)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; N = number of patients; n = number of patients in specific category; NSCLC = non-small cell lung cancer; *RET* = REarranged during Transfection.

a Patient demographics for The First 105 Patients with Prior Platinum Chemotherapy Analysis Set is provided in Table 8.7.

b The total column is calculated from the Prior Platinum Chemotherapy, Treatment-Naïve, Prior Other Systemic Therapy, and Non-Measurable Disease Analysis Sets.

Baseline Disease Characteristics

Table 12: Baseline Disease Characteristics - RET Fusion Positive NSCLC Efficacy Analysis Population (Data Cutoff: 15 June 2021)

Analysis Set	Prior Platinum Chemotherapy (N=247)	Treatment-Naïve (N=69)	Supportive Analysis Sets[a]		Total[b] (N=355)
			Prior Other Systemic Therapy (N=19)	Non-Measurable Disease (N=20)	
Primary tumor type, n (%)					
NSCLC	247 (100.0)	69 (100.0)	19 (100.0)	20 (100.0)	355 (100.0)
Time since initial diagnosis, months					
Median	21.90	2.00	8.30	18.90	16.30
Range	1.2-194.3	0.5-21.9	2.0-112.5	7.4-223.7	0.5-223.7
Investigator reported history of metastatic disease, n (%)					
Yes	240 (97.2)	68 (98.6)	19 (100.0)	20 (100.0)	347 (97.7)
No	7 (2.8)	1 (1.4)	0 (0.0)	0 (0.0	8 (2.3)
Months since metastatic disease					
Median	18.15	1.60	8.30	10.80	10.90
Range	1.0-158.5	0-8.1	2.0-75.5	0.4-91.1	0-158.5
At least 1 measurable lesion by investigator, n (%)					
Yes	246 (99.6)	69 (100.0)	19 (100.0)	0	334 (94.1)
No	1[c] (0.4)	0 (0.0)	0 (0.0)	20 (100.0)	21 (5.9)
Sum of diameters at baseline by investigator, mm					
Median	51.130	69.500	75.000	NA	56.000
Range	10.00-297.00	11.00-191.00	12.00-249.60	NA	10.00-297.00
CNS metastases at baseline by investigator, n (%)					
Yes	77 (31.2)	16 (23.2)	11 (57.9)	2 (10.0)	106 (29.9)
No	170 (68.8)	53 (76.8)	8 (42.1)	18 (90.0)	249 (70.1)

Abbreviations: CNS = central nervous system; N = number of patients; n = number of patients in specific category; NSCLC = non-small cell lung cancer; RET = REarranged during Transfection.

a Baseline disease characteristics for The First 105 Patients with Prior Platinum Chemotherapy Analysis Set is summarized in Table 8.9and Table 8.10.

b The total column is calculated from the Prior Platinum Chemotherapy, Treatment-Naïve, Prior Other Systemic Therapy, and Non-Measurable Disease Analysis Sets.

c Patient was enrolled in Phase 1.

Table 13: Baseline Disease Characteristics – RET Fusion Status RET Fusion-Positive NSCLC Efficacy Analysis Population (Data Cutoff: 15 June 2021)

Analysis Set	Prior Platinum Chemotherapy (N=247)	Treatment-Naïve (N=69)	Supportive Analysis Sets[a]		Total[b] (N=355)
			Prior Other Systemic Therapy (N=19)	Non-Measurable Disease (N=20)	
***RET* fusion partner, n(%)**					
KIF5B	153 (61.9)	48 (69.6)	14 (73.7)	12 (60.0)	227 (63.9)
CCDC6	53 (21.5)	10 (14.5)	3 (15.8)	5 (25.0)	71 (20.0)
NCOA4	5 (2.0)	1 (1.4)	1 (5.3)	1 (5.0)	8 (2.3)
Other	16 (6.5)	2 (2.9)	1 (5.3)	0 (0.0)	19 (5.4)
Unknown	22 (8.9)	8 (11.6)	0 (0.0)	2 (10.0)	32 (9.0)
Molecular Assay Type, n (%)					
NGS on Tumor	209 (84.6)	42 (60.9)	16 (84.2)	17 (85.0)	284 (80.0)
PCR on Tumor	4 (1.6)	1 (1.4)	1 (5.3)	0	6 (1.7)
NGS on Plasma/Blood	23 (9.3)	21 (30.4)	2 (10.5)	3 (15.0)	49 (13.8)
FISH on Tumor	10 (4.0)	5 (7.2)	0 (0.0)	0 (0.0)	15 (4.2)
Other[c]	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Abbreviations: FISH =Fluorescence in situ hybridization ; N = number of patients; n = number of patients in specific category; NGS = next generation sequencing; NSCLC = non-small cell lung cancer; PCR = polymerase chain reaction; RET = REarranged during Transfection.

a *RET* fusion status for The First 105 Patients with Prior Platinum Chemotherapy Analysis Set is summarized in Table 8.10.

b Total column is calculated from the Prior Platinum Chemotherapy, Treatment-Naïve, Prior Other Systemic Therapy, and Non-Measurable Disease Analysis Sets.

c Other molecular assay type is Nanostring Technology

Table 14: Prior Cancer Therapy RET Fusion-Positive NSCLC Efficacy Analysis Population (Data Cutoff: 15 June 2021)

Analysis Set	Prior Platinum Chemotherapy (N = 247)	Treatment-Naïve (N = 69)	Supportive Analysis Sets[a]		Total[b] (N = 355)
			Prior Other Systemic Therapy (N = 19)	Non-Measurable Disease (N = 20)	
Received prior systemic therapy, n (%)					
Yes	247 (100.0)	NA	19 (100.0)	20 (100.0)	286 (80.6)
No	0 (0.0)	69 (100.0)	0 (0.0)	0 (0.0)	69 (19.4)
Type of prior systemic therapy[c], n (%)					
Chemotherapy	247 (100.0)	NA	1 (5.3)	20 (100.0)	268 (75.5)
Platinum chemotherapy	247 (100.0)	NA	0	19 (95.0)	266 (74.9)
Immunotherapy	145 (58.7)	0	13 (68.4)	9 (45.0)	167 (47.0)
Anti-PD-1/PD-L1 therapy	144 (58.3)	NA	13 (68.4)	9 (45.0)	166 (46.8)
Anti CTLA4 therapy	6 (2.4)	NA	2 (10.5)	0	8 (2.3)
Multikinase inhibitor	85 (34.4)	0 (0.0)	8 (42.1)	5 (25.0)	98 (27.6)
Cabozantinib	25 (10.1)	NA	3 (15.8)	2 (10.0)	30 (8.5)
Vandetanib	12 (4.9)	NA	1 (5.3)	1 (5.0)	14 (3.9)
Sorafenib	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)
Lenvatinib	8 (3.2)	NA	1 (5.3)	1 (5.0)	10 (2.8)
Other MKIs	61 (24.7)	NA	4 (21.1)	2 (10.0)	67 (18.9)
Other[d]	97 (39.3)	0	3 (15.8)	7 (35.0)	107 (30.1)
VEGF/VEGFR inhibitor	79 (32.0)	NA	0 (0.0)	4 (20.0)	83 (23.4)
EGFR inhibitor	13 (5.3)	NA	1 (5.3)	1 (5.0)	15 (4.2)
Number of prior systemic regimens, n (%)					
0	0	69 (100.0)	0 (0.0)	0 (0.0)	69 (19.4)
1	73 (29.6)	NA	14 (73.7)	7 (35.0)	94 (26.5)
2	67 (27.1)	NA	3 (15.8)	5 (25.0)	75 (21.1)
≥3	107 (43.3)	NA	2 (10.5)	8 (40.0)	117 (33.0)
Number of prior systemic regimens					
Median	2.0	NA	1.0	2.0	2.0
Range	1-15	NA	1-5	1-9	0-15
Best response to last systemic treatment, n (%)					
Complete response	2 (0.8)	NA	0	0	2 (0.6)
Partial response	36 (14.6)	NA	1 (5.3)	NA	37 (10.4)
Stable disease	74 (30.0)	NA	2 (10.5)	6 (30.0)	82 (23.1)
Progressive disease	71 (28.7)	NA	11 (57.9)	5 (25.0)	87 (24.5)
Not evaluated	62 (25.1)	NA	5 (26.3)	9 (45.0)	76 (21.4)
Unknown[e]	2 (0.8)	69 (100.0)	0 (0.0)	0 (0.0)	71 (20.0)
Prior radiotherapy, n (%)					
Yes	132 (53.4)	23 (33.3)	10 (52.6)	13 (65.0)	178 (50.1)
No	115 (46.6)	46 (66.7)	9 (47.4)	7 (35.0)	177 (49.9)
Prior cancer related surgery, n (%)					
Yes	110 (44.5)	17 (24.6)	9 (47.4)	13 (65.0)	149 (42.0)
No	137 (55.5)	52 (75.4)	10 (52.6)	7 (35.0)	206 (58.0)

Dose intensity

Table 15: Selpercatinib Dose Intensity Overall Safety Population and NSCLC Safety Population (Data Cutoff: 15 June 2021)

	NSCLC Safety Population (N=356)	Overall Safety Population (N=796)
Time on Treatment (months)		
Median	19.09	21.29
Minimum	0.1	0.1
Maximum	49.0	49.0
Relative Dose Intensity (%)		
Mean (standard deviation)	83.36 (19.9)	84.64 (19.1)
Median	92.71	94.46
Range	21.3, 100.1	17.3, 100.1
Relative Dose Intensity Categories, n (%)		
≥90%	197 (55.3)	466 (58.5)
75 to <90%	62 (17.4)	122 (15.3)
50 to <75%	64 (18.0)	146 (18.3)
<50%	33 (9.3)	62 (7.8)

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

Dose Modification and Compliance

Table 16: Dose Modifications in NSCLC and Overall Safety Populations (Data Cutoff: 15 June 2021)

	NSCLC Safety Population (N=356)	Overall Safety Population (N=796)
Dose reduction, n (%)		
Any	180 (50.6)	343 (43.1)
For AE	172 (48.3)	325 (40.8)
For other reason	22 (6.2)	47 (5.9)
Dose withheld, n (%)		
Any	276 (77.5)	580 (72.9)
For AE	245 (68.8)	510 (64.1)
For other reason	103 (28.9)	229 (28.8)
Dose increase, n (%)		
Any	102 (28.7)	183 (23.0)
Intra-patient escalation[a]	36 (10.1)	69 (8.7)
Re-escalation[b]	51 (14.3)	84 (10.6)
Other reason	27 (7.6)	52 (6.5)

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

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

[b] Re-escalation after a dose reduction.

Numbers analysed

At the DCO date, all 355 patients with RET fusion-positive NSCLC from Cohorts 1, 2, and 5 are included in the efficacy analysis as they had achieved at least 6 months of potential follow-up time from the first dose.

The primary efficacy analysis set to support the proposed first-line indication included 69 Treatment-Naïve Patients (previously named SAS1);

The main supportive analysis sets include:

- Patients Previously Treated with Platinum-Based Chemotherapy (N=247) (previously named IAS);
- CNS Response Analysis Set (N=106).

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

Outcomes and estimation

Treatment-Naïve Patients with RET Fusion-Positive NSCLC

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

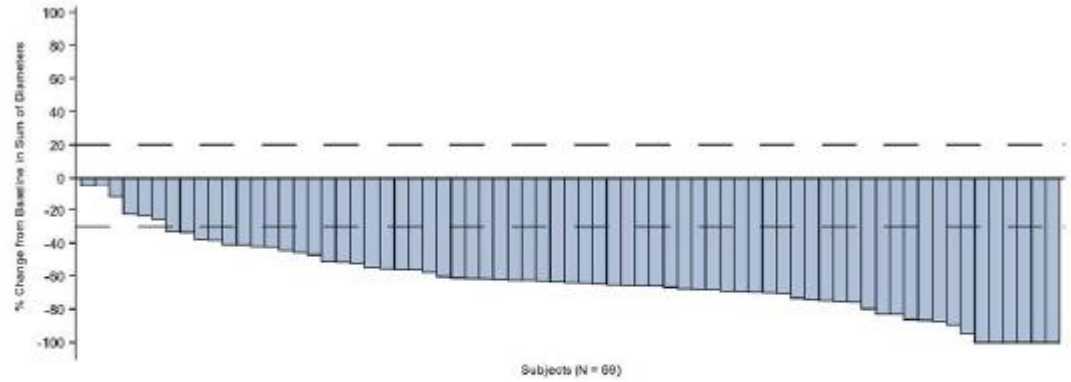
Table 17: Objective Response Rate, Best Overall Response, and Clinical Benefit Rate Based on IRC and Investigator Assessment Treatment-Naïve Patients (Data Cutoff Date: 15 June 2021)

	IRC Assessment (N=69)	Investigator Assessment (N=69)
Objective Response Rate[a]		
n (%)	58 (84.1)	59 (85.5)
95% CI	(73.3, 91.8)	75.0, 92.8
Best Overall Response – no. (%)		
Complete response (CR)	4 (5.8)	1 (1.4)
Partial response (PR)	54 (78.3)	58 (84.1)
Stable disease (SD)	6 (8.7)	5 (7.2)
SD≥16 weeks[c]	6 (8.7)	4 (5.8)
Progressive disease (PD)	3 (4.3)	3 (4.3)
Not evaluable	2 (2.9)	2 (2.9)
Clinical Benefit Rate (CR + PR + SD≥)[d]		
n (%)	64 (92.8)	63 (91.3)
95% CI[b]	(83.9, 97.6)	(82.0, 96.7)
Duration of Response (months)[e,f]		
Median (95% CI)	20.21 (13.0, NE)	20.27 (14.8, NE)
Censored	32 (55.2)	31 (52.5)
Duration of Follow-Up (months)[e]		
Median	20.27	23.03
25th, 75th percentiles	12.9, 26.7	15.2, 26.5
Rate (%) of Duration of Response[e,g]		
≥6 months (95% CI)	87.7 (75.9, 93.9)	86.2 (74.3, 92.9)
≥12 months (95% CI)	66.1 (51.6, 77.3)	66.3 (52.4, 77.1)
≥24 months (95% CI)	41.6 (25.6, 56.8)	41.8 (26.1, 56.7)
≥36 months (95% CI)	41.6 (25.6, 56.8)	41.8 (26.1, 56.7)

Eligible patients are treated on or before 15 December 2020. Stable disease includes Non-CR/Non-PD.
Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; N = number of patients; n = number of patients in specific category; NE = not estimable; No. = number; ORR = objective response rate; PR = partial response; SD = stable disease.

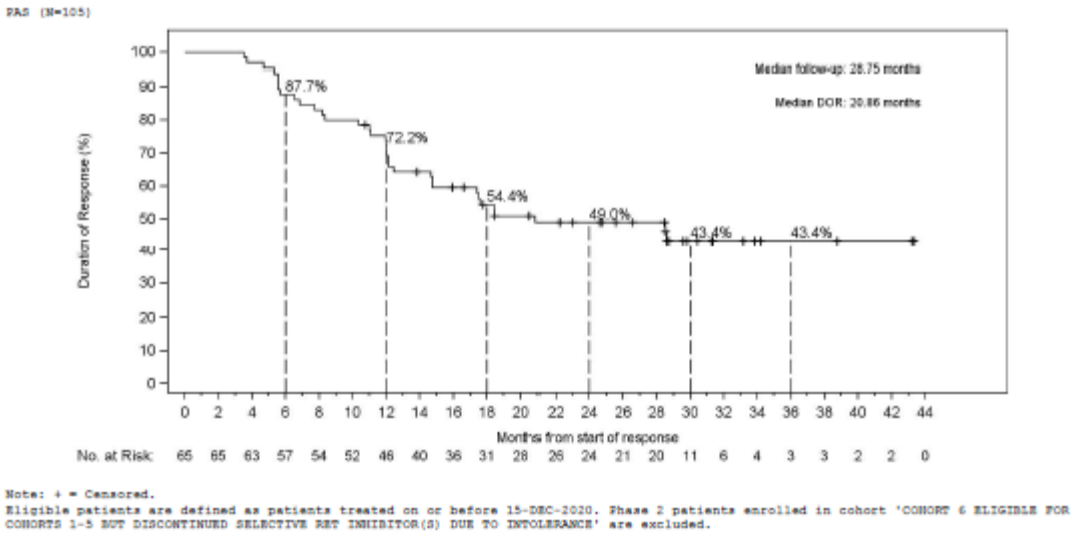
a ORR is defined as the proportion of patients with best overall response of confirmed CR or PR. Response was confirmed by a repeat assessment ≥ 28 days.
b 95% CI was calculated using Clopper-Pearson method.
c Indicates SD lasting ≥ 16 weeks following initiation of selpercatinib until the criteria for disease progression was first met.
d Clinical benefit rate (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or SD lasting 16 or more weeks (SD*). Stable disease was measured from the date of the first dose selpercatinib until the criteria for disease progression was first met.

Figure 5. Waterfall plot of best change in tumour burden based on IRC assessments – Treatment naïve patients (Data cut-off: 15 June 2021)



Eligible patients are defined as patients treated on or before 15 December 2020.
For each subject, the best percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar. The dashed lines represent the RECIST v1.1. criteria for response (30% decrease) or progressive disease (20% increase).
Abbreviations: IRC = Independent Review Committee; RECIST = Response Evaluation Criteria in Solid Tumors.

Figure 6. Kaplan-Meier Plot of Duration of Response Based on IRC Assessments – Efficacy Eligible Subjects of RET fusion-positive NSCLC with confirmed CR or PR



Note: + = Censored.
Eligible patients are defined as patients treated on or before 15-DEC-2020. Phase 2 patients enrolled in cohort 'COHORT 6 ELIGIBLE FOR COHORTS 1-5 BUT DISCONTINUED SELECTIVE RET INHIBITOR(S) DUE TO INTOLERANCE' are excluded.

Time to Response and Time to Best Response

Table 18: Time to Response and Based on IRC and Investigator's Assessments Treatment-Naïve Patients (Data Cutoff Date: 15 June 2021)

Status	IRC Assessment (N=69)	Investigator Assessment (N=69)
Time to Response (months)		
Median	1.81	1.81
25th, 75th Percentiles	1.7, 3.4	1.7, 1.9
Minimum, Maximum	0.7, 10.8	0.8, 5.6
Time to Response, n (%)		
<2 months	41 (70.7)	46 (78.0)
≥2 to 4 months	15 (25.9)	9 (15.3)
≥4 to 6 months	0 (0.0)	4 (6.8)
≥6 to 9 months	1 (1.7)	0 (0.0)
≥9 months	1 (1.7)	0 (0.0)
Time to Best Response (months)		
Median	1.82	1.84
25th, 75th percentiles	1.7, 3.5	1.7, 1.9
Min, max	0.7, 24.8	0.8, 5.6
Time to Best Response, n (%)		
<2 months	39 (67.2)	45 (76.3)
≥2 to 4 months	14 (24.1)	10 (16.9)
≥4 to 6 months	0 (0.0)	4 (6.8)
≥6 to 9 months	1 (1.7)	0 (0.0)
≥9 months	4 (6.9)	0 (0.0)

Abbreviations: IRC = Independent Review Committee; max = maximum; min = minimum; N = number of patients; n = number of patients in specific category.

Progression-free Survival

Status	IRC Assessment (N=69)	Investigator Assessment (N=69)
Progression Status, n (%)[a]		
Disease progression	29 (42.0)	34 (49.3)
Died (no disease progression beforehand)	3 (4.3)	2 (2.9)
Censored	37 (53.6)	33 (47.8)
Duration of Progression-Free Survival (months)[b,c]		
Median	21.95	20.73
95% CI for median	13.8, NE	13.6, NE
Min, max	0.0+, 41.0+	0.0+, 41.0+
Duration of Follow-Up (months)[b]		
Median	21.91	24.67
25th, 75th percentiles	13.8, 27.6	18.7, 27.6
Rate (%) of Progression-Free Survival[b,d]		
≥6 months (95% CI)	86.6 (75.8, 92.8)	84.9 (73.8, 91.6)
≥12 months (95% CI)	70.6 (57.8, 80.2)	66.4 (53.5, 76.4)
≥24 months (95% CI)	41.6 (26.8, 55.8)	44.1 (30.8, 56.5)
≥36 months (95% CI)	38.4 (23.8, 52.9)	36.0 (21.9, 50.4)

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

Abbreviations: CI = confidence interval; IRC = Independent Review Committee; N = number of patients; n = number of patients in specific category; NE = not estimable; NSCLC = non-small cell lung cancer; RET = REarranged during Transfection; SD = stable disease.

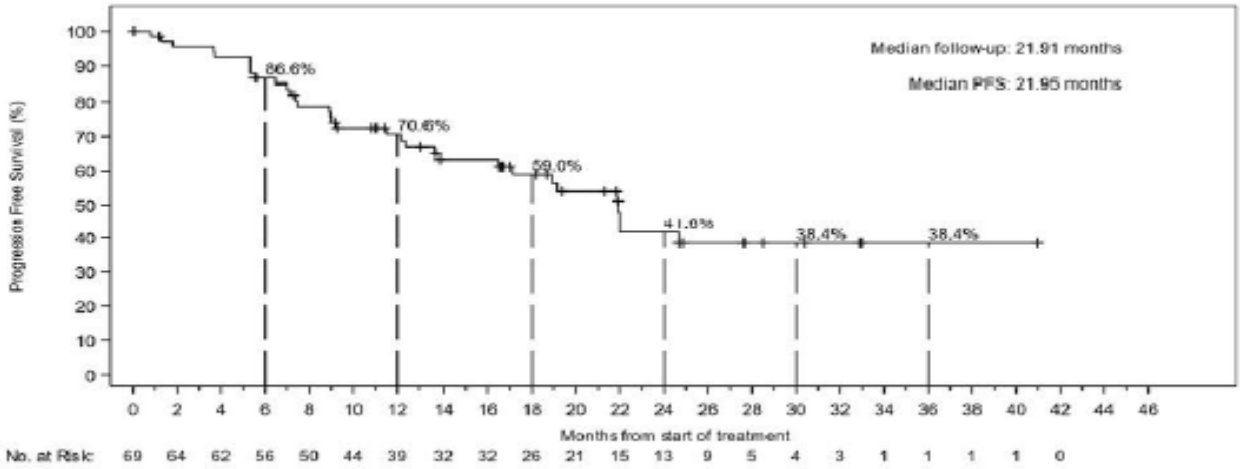
a Status as of the patient's last disease assessment on or before 15 June 2021.

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

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

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

Figure 7. Kaplan-Meier plot of progression-free survival based on IRC assessments – Treatment naïve patients (Data cutoff: 15 June 2021)



Abbreviations: IRC = Independent Review Committee; PFS = progression-free survival.

Overall Survival

Table 19: Overall Survival Treatment-Naïve Patients (Data Cutoff Date: 15 June 2021)

Status	Treatment-Naïve Patients (N=69)
Survival Status n (%)	
Dead	20 (29.0)
Censored	49 (71.0)
Duration of Overall Survival (months) [a,b]	
Median	NE
95% CI for median	27.9, NE
Min, max	1.4, 41.9+
Duration of Follow-up (months) [a]	
Median	25.20
25th, 75th percentiles	17.9, 29.4
Rate (%) of Overall Survival[a,b]	
≥12 months (95% CI)	92.7 (83.3, 96.9)
≥24 months (95% CI)	69.3 (55.2, 79.7)
≥36 months (95% CI)	57.1 (35.9, 73.6)

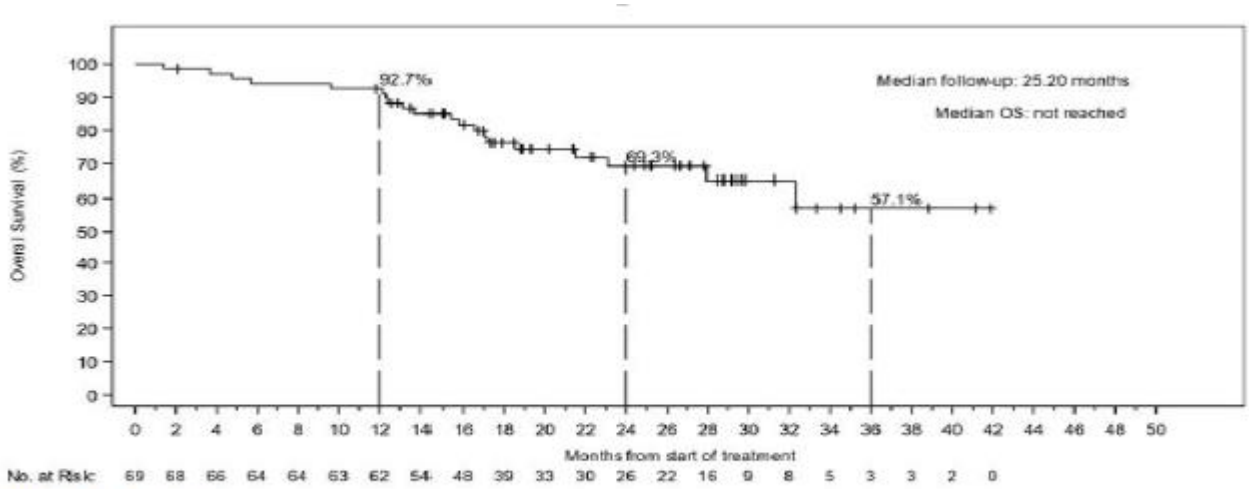
Status as of the last contact on or before 15 June 2021.

Abbreviations: CI = confidence interval; max = maximum; min = minimum; N = number of participants in the specified category; NE = not estimable.

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

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

Figure 8: Kaplan-Meier plot of OS in treatment naïve patients (DCO: 15 June 2021)



Note: + = Censored.
Eligible patients are defined as patients treated on or before 15 December 2020.
Abbreviations: OS = overall survival.

Patients with RET Fusion-Positive NSCLC Previously Treated with Platinum-Based Chemotherapy

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

Table 20: Objective Response Rate, Best Objective Response, Duration of Response, and Clinical Benefit Rate Based on IRC and Investigator Assessments (Data Cutoff Date: 15 June 2021)

	IRC Assessment (N=247)	Investigator Assessment (N=247)
Objective Response Rate[a,b]		
n (%)	151 (61.1)	159 (64.4)
95% CI	(54.7, 67.2)	(58.1, 70.3)
Best Overall Response – n (%)		
Complete response (CR)	18 (7.3)	9 (3.6)
Partial response (PR)	133 (53.8)	150 (60.7)
Stable disease (SD)	81 (32.8)	74 (30.0)
SD -16 weeks[c]	60 (24.3)	55 (22.3)
Progressive disease (PD)	7 (2.8)	5 (2.0)
Not evaluable	8 (3.2)	9 (3.6)
Clinical Benefit Rate (CR + PR + SD-16 weeks[c])[d]		
n (%)	211 (85.4)	214 (86.6)
95% CI[b]	(80.4, 89.6)	(81.8, 90.6)
Duration of Response (months)[e,f]		
Median (95% CI)	28.58 (20.4, NE)	21.22 (18.4, 31.8)
Censored n (%)	92 (60.9)	80 (50.3)
Duration of Follow-Up (months)[e]		
Median	21.19	23.20
25th, 75th percentiles	16.6, 26.0	20.3, 29.5
Rate (%) of Duration of Response[e,g]		
≥6 months (95% CI)	86.9 (80.3, 91.5)	89.2 (83.2, 93.1)
≥12 months (95% CI)	73.1 (64.9, 79.7)	73.4 (65.6, 79.6)
≥24 months (95% CI)	55.8 (46.4, 64.2)	46.2 (37.3, 54.7)
≥36 months (95% CI)	49.4 (37.5, 60.3)	26.3 (12.1, 42.8)

Eligible patients were treated on or before 15 December 2020. Stable disease includes non-CR/non-PD.

Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; N = number of patients; n = number of patients in specific category; NE = not estimable; No. = number; NSCLC = non-small cell lung cancer; ORR = objective response rate; PR = partial response; SD = stable disease.

a ORR is defined as the proportion of patients with best overall response of confirmed CR or PR. Response was confirmed by a repeat assessment ≥ 28 days.

b 95% CI was calculated using Clopper-Pearson method

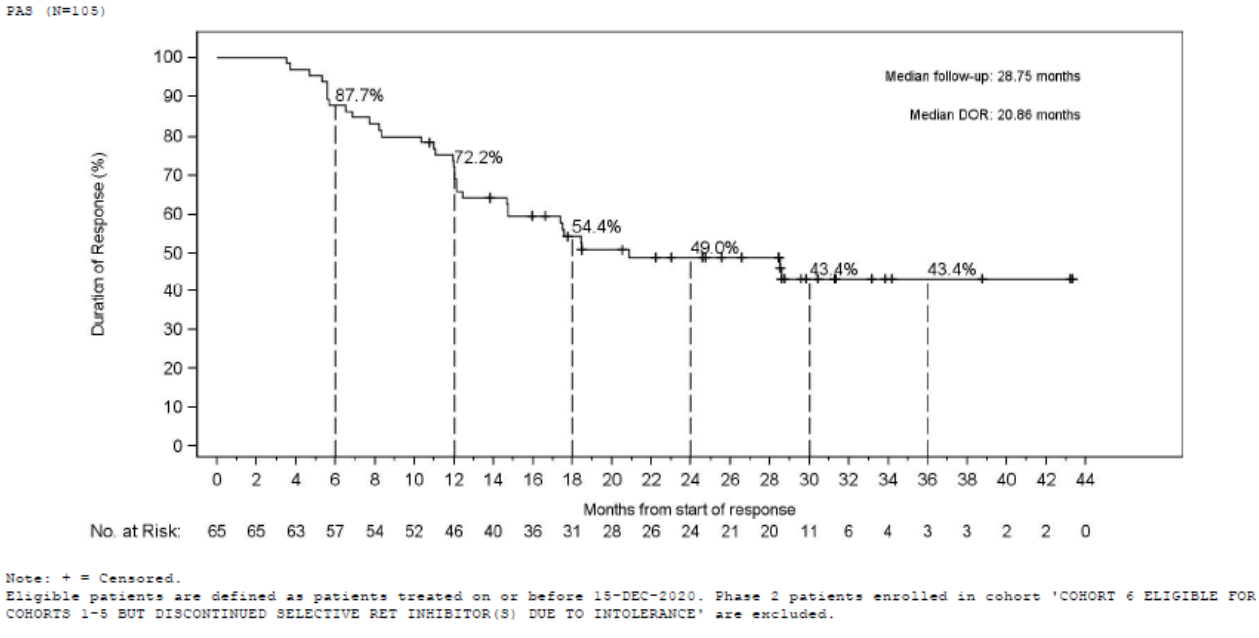
c Indicates SD lasting ≥ 16 weeks following initiation of selpercatinib until the criteria for disease progression was first met.

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

e Estimate based on Kaplan-Meier method.

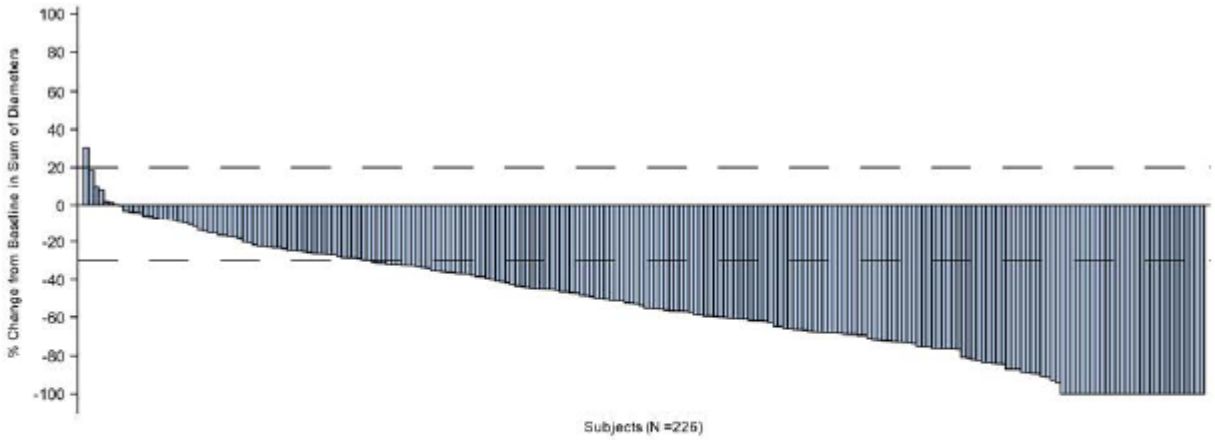
f 95% CI was calculated using Brookmeyer and Crowley method.

Figure 9. Kaplan-Meier Plot of Duration of Response Based on IRC Assessments – Efficacy Eligible Subjects of RET fusion-positive NSCLC with Confirmed CR of PR



Note: + = Censored.
Eligible patients are defined as patients treated on or before 15-DEC-2020. Phase 2 patients enrolled in cohort 'COHORT 6 ELIGIBLE FOR COHORTS 1-5 BUT DISCONTINUED SELECTIVE RET INHIBITOR(S) DUE TO INTOLERANCE' are excluded.

Figure 10: Waterfall plot of best change in tumour burden based on IRC assessments Patients previously treated with platinum-based chemotherapy



For each subject, the best percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar. The dashed lines represent the RECIST v1.1. criteria for response (30% decrease) or progressive disease (20% increase).

Note: Twenty-one subjects are not included because 16 subjects have non-target lesion only and 5 do not have postbaseline target lesion measurement.

Abbreviations: IRC = Independent Review Committee; RECIST = Response Evaluation Criteria in Solid Tumors.

-Time to response and Time to Best Response

Table 21: Time to Response in Patients Previously Treated with Platinum-Based Chemotherapy Based on IRC and Investigator Assessments

Status	IRC Assessment (N=247)	Investigator Assessment (N=247)
Time to Response (months)[a]		
Median	1.87	1.84
25th, 75th Percentiles	1.8, 3.8	1.7, 2.1
Minimum, Maximum	0.7, 21.9	0.7, 35.3
Time to Response, n (%)		
<2 months	92 (60.9)	115 (72.3)
≥2 to 4 months	24 (15.9)	28 (17.6)
≥4 to 6 months	16 (10.6)	6 (3.8)
≥6 to 9 months	6 (4.0)	3 (1.9)
≥9 months	13 (8.6)	7 (4.4)
Time to Best Response (months)[b]		
Median	1.87	1.84
25th, 75th percentiles	1.8, 5.4	1.7, 3.6
Min, max	0.7, 32.9	0.7, 35.3
Time to Best Response, n (%)		
<2 months	85 (56.3)	109 (68.6)
≥2 to 4 months	25 (16.6)	29 (18.2)
≥4 to 6 months	16 (10.6)	9 (5.7)
≥6 to 9 months	7 (4.6)	4 (2.5)
≥9 months	18 (11.9)	8 (5.0)

Abbreviations: CR = complete response; IRC = Independent Review Committee; max = maximum; min = minimum; PR = partial response.

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

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

Progression-Free Survival

Table 22: Progression-Free Survival Patients Previously Treated with Platinum-Based Chemotherapy Based on IRC and Investigator Assessments

Status	IRC Assessment (N=247)	Investigator Assessment (N=247)
Progression Status, n (%)[a]		
Disease progression	89 (36.0)	116 (47.0)
Died (no disease progression beforehand)	20 (8.1)	16 (6.5)
Censored	138 (55.9)	115 (46.6)
Duration of Progression-Free Survival (months)[b,c]		
Median	24.94	21.75
95% CI for median	19.3, NE	16.8, 24.9
Min, max	0.0+, 44.2+	0.0+, 44.2+
Duration of Follow-Up (months)[b]		
Median	24.71	24.94
25th, 75th percentiles	19.3, 28.7	22.1, 30.4
Rate (%) of Progression-free Survival[b,d]		
≥6 months (95% CI)	83.7 (78.4, 87.9)	82.6 (77.1, 86.9)
≥12 months (95% CI)	70.5 (64.1, 76.0)	67.0 (60.5, 72.6)
≥24 months (95% CI)	51.4 (44.3, 58.1)	44.9 (38.1, 51.5)
≥36 months (95% CI)	42.6 (33.4, 51.6)	30.1 (19.5, 41.4)

Abbreviations: CI = confidence interval; IRC = Independent Review Committee; max = maximum; min = minimum; N = number of patients; n = number of patients in specific category; NE = not estimable.

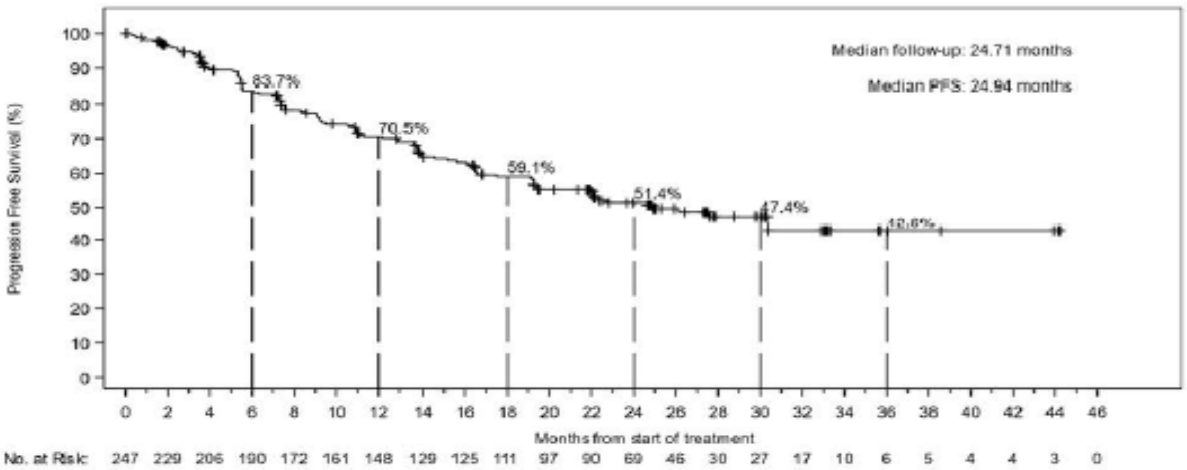
a Status as of the patient's last disease assessment on or before 15 June 2021.

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

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

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

Figure 11. Kaplan-Meier Plot of Progression-Free Survival



Note: + = Censored.

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

Abbreviation: IRC = Independent Review Committee; No. = number; PFS = progression-free survival.

Overall Survival

Table 23: Overall Survival Patients Treated with Platinum-Based Chemotherapy

Status	Patients with *RET* Fusion-Positive NSCLC Previously Treated with Platinum-based Chemotherapy (N=247)
Survival Status n (%)[a]	
Dead	78 (31.6)
Censored	169 (68.4)
Reason Censored (n, %)	
Lost to Follow-up	1 (0.4)
OS Follow-up Ongoing	143 (57.9)
Withdrawal of Consent	25 (10.1)
Duration of Overall Survival (months)[b,c]	
Median	NE
95% CI for median	33.5, NE
Min, max	0.3, 49.0+
Duration of Follow-up (months)[b]	
Median	26.41
25th, 75th percentiles	22.0, 31.3
Rate (%) of Overall Survival[b,d]	
≥12 months (95% CI)	87.9 (83.0, 91.4)
≥24 months (95% CI)	68.9 (62.2, 74.7)
≥36 months (95% CI)	58.5 (49.7, 66.3)

Abbreviations: CI = confidence interval; max = maximum; min = minimum; N = number of participants in the specified category; n = number of patients in specific category; NE = not estimable; NSCLC = non-small cell lung cancer; OS = overall survival; RET = REarranged during Transfection.

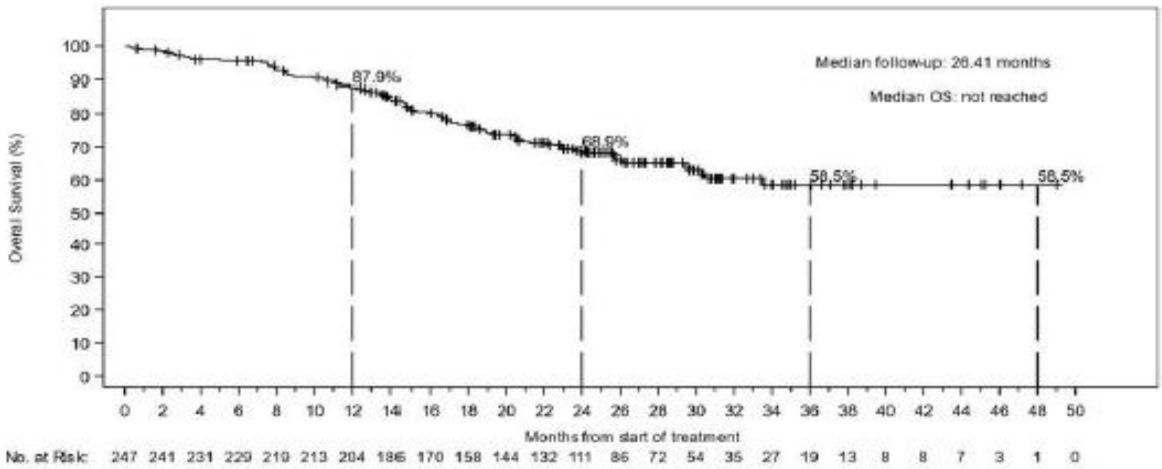
a Status as of the last contact on or before 15 June 2021.

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

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

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

Figure 12. Kaplan-Meier plot of overall survival

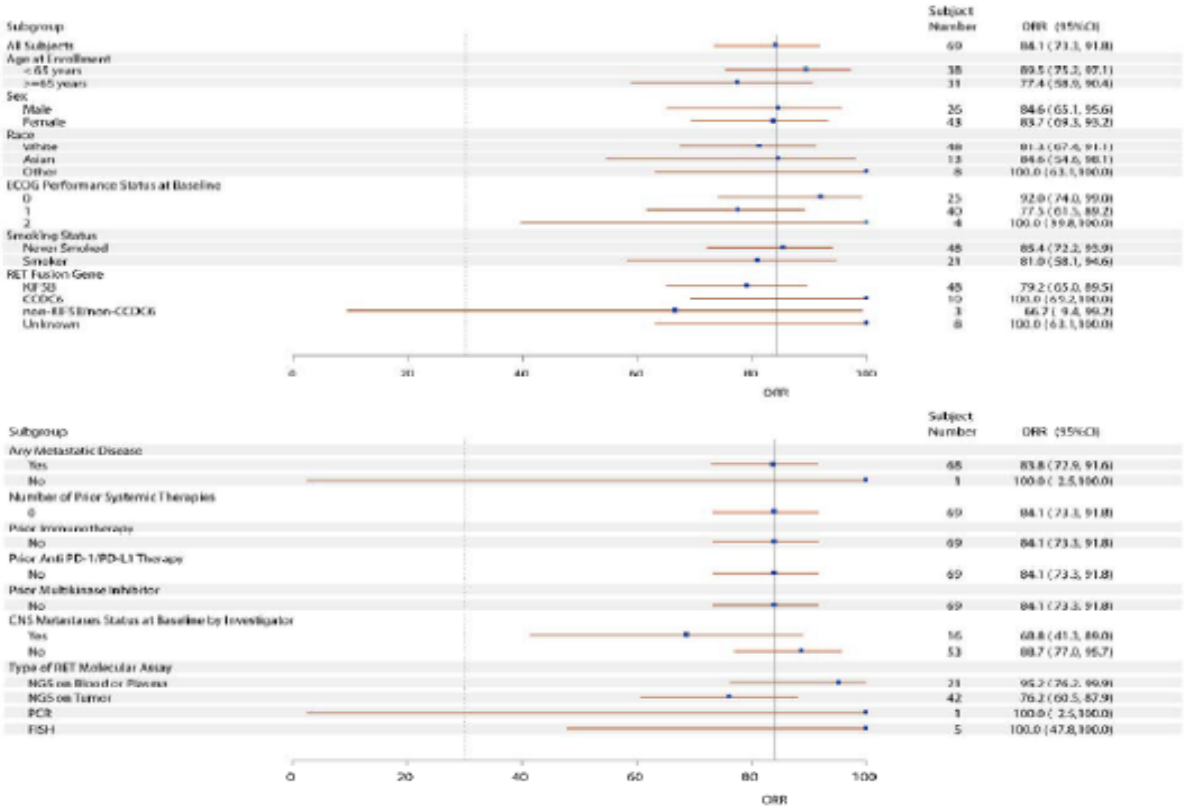


Note: + = Censored.
Eligible patients are defined as patients treated on or before 15 December 2020.
Abbreviations: No. = number; OS = overall survival.

Ancillary analyses

Treatment-Naïve Patients with RET Fusion-Positive NSCLC

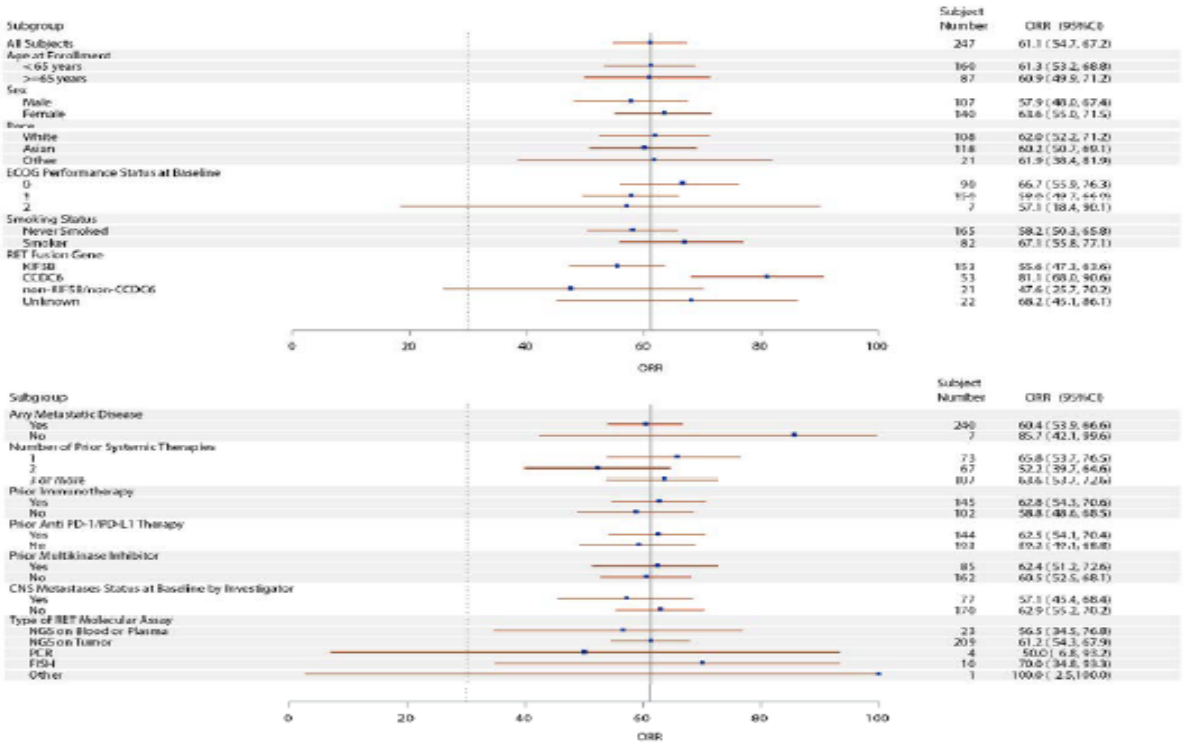
Figure 13: Forest plot of objective response rate in special/subgroup populations by demography and baseline characteristics based on IRC assessments in Treatment-naïve patients with RET Fusion positive NSCLC



Two-sided 95% exact binomial CI is calculated using the Clopper-Pearson method.
Dashed reference line = 30%, solid reference line = 84.1% (overall ORR).
Abbreviations: CI = confidence interval; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; FISH = Fluorescence in situ hybridization; IRC = Independent Review Committee; NGS = next generation sequencing; ORR = objective response rate; PCR = polymerase chain reaction; PD-1 = programmed cell death 1 receptor; PD-L1 = programmed cell death receptor ligand 1; RET = REarranged during Transfection.

Patients with RET Fusion-Positive NSCLC Previously Treated with Platinum-Based Chemotherapy

Figure 14: Forest plot of objective response rate in special/subgroup populations by demography and baseline characteristics based on IRC assessments in Patients Previously Treated with Platinum- Based Chemotherapy



Two-sided 95% exact binomial CI is calculated using the Clopper-Pearson method.
Dashed reference line = 30%, solid reference line = 61.1% (overall ORR).
Abbreviations: CI = confidence interval; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; FISH = Fluorescence in situ hybridization; IRC = Independent Review Committee; NGS = next generation sequencing; ORR = objective response rate; PCR = polymerase chain reaction; PD-1 = programmed cell death 1 receptor; PD-L1 = programmed cell death receptor ligand 1; RET = REarranged during Transfection.

Prior Immunotherapy

Among the 247 patients with RET fusion-positive NSCLC previously treated with platinum based chemotherapy, 58.7% patients (145/247) also received prior immunotherapy, either sequentially or concurrently with platinum-based chemotherapy.

The immunotherapies received by the patients previously treated with platinum-based therapy were:

-Anti-PD1/PD-L1 therapy by 144 patients (58.3%), and

-Anti CTLA4 therapy by 6 patients (2.4%).

Table 24: BOR, ORR, CBR, DOR, and PFS Based on IRC Assessments by Prior Immunotherapy (Data Cutoff Date: 15 June 2021)

Response	Prior Platinum-Based Chemotherapy	
	With Prior Immunotherapy	Without Prior Immunotherapy
	N=145	N=102
Objective Response Rate[a]		
n (%)	91 (62.8)	60 (58.8)
95% CI	(54.3, 70.6)	(48.6, 68.5)
Best Overall Response – no. (%)		
Complete response (CR)	9 (6.2)	9 (8.8)
Partial response (PR)	82 (56.6)	51 (50.0)
Stable disease (SD)	42 (29.0)	39 (38.2)
SD[c]	26 (17.9)	34 (33.3)
Progressive disease (PD)	6 (4.1)	1 (1.0)
Not evaluable	6 (4.1)	2 (2.0)
Clinical Benefit Rate (CR + PR + SD[b]) [a]		
n (%)	117 (80.7)	94 (92.2)
95% CI	(73.3, 86.8)	(85.1, 96.6)
Patients with Best Response of Confirmed CR or PR	91	60
Response Status (n, %)[e]		
Disease Progression	33 (36.3)	19 (31.7)
Died (No Disease Progression Beforehand)	5 (5.5)	2 (3.3)
Censored	53 (58.2)	39 (65.0)
Duration of Response (months)[d]		
Median (95% CI for median)	28.58 (14.8, NE)	NR (20.4, NE)
Min, max	1.8+, 38.8+	2.7+, 43.3+
Duration of Follow-up (months)[c]		
Median	20.50	23.03
25th, 75th Percentiles	16.4, 26.0	16.6, 28.7
Duration of Progression-Free Survival (months)[c,d]		
Median (95% CI for median)	19.35 (13.9, 27.6)	NE (22.1, NE)
Min, max	0.3, 44.2+	0.0+, 44.2+

Abbreviations: BOR = best overall response; CBR = clinical benefit rate; CI = confidence interval; DOR = duration of response; IRC = Independent Review Committee; max = maximum; min = minimum; N = number of patients; n = number of patients in specific category; NE = not estimable; ORR = objective response rate; PFS = progression-free survival.

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

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

c Estimate based on Kaplan-Meier method. NE = Not estimable. NR = Not reached. + = Censored observation.

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

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

Table 25 Objective Response Rate, Best Overall Response, and Clinical Benefit Rate Based on IRC and Investigator Assessment Supportive Efficacy Analysis Sets

Status	Patients with *RET* Fusion-Positive NSCLC Previously Treated with Other Systemic Therapy (N=19)		Patients with Non-Measurable *RET* Fusion-Positive NSCLC (N=20)		First 105 Patients Enrolled with *RET* Fusion-Positive NSCLC Who Were Previously Treated with Platinum-Based Chemotherapy[h] (N=105)	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
Objective Response Rate[a,b] (CR + PR)						
n (%)	9 (47.4)	12 (63.2)	8 (40.0)	0 (0.0)	65 (61.9)	74 (70.5)
95% CI	(24.4, 71.1)	(38.4, 83.7)	(19.1, 63.9)	(0.0, 16.8)	(51.9, 71.2)	(60.8, 79.0)
Best Overall Response, n (%)						
CR	0 (0.0)	0 (0.0)	3 (15.0)	0 (0.0)	4 (3.8)	3 (2.9)
PR	9 (47.4)	12 (63.2)	5 (25.0)	0 (0.0)	61 (58.1)	71 (67.6)
SD	9 (47.4)	5 (26.3)	9 (45.0)	20 (100.0)	32 (30.5)	24 (22.9)
SD≥16 weeks[c]	4 (21.1)	1 (5.3)	8 (40.0)	16 (80.0)	24 (22.9)	17 (16.2)
PD	1 (5.3)	2 (10.5)	0 (0.0)	0 (0.0)	4 (3.8)	3 (2.9)
NE	0 (0.0)	0 (0.0)	3 (15.0)	0 (0.0)	4 (3.8)	4 (3.8)
Clinical Benefit Rate (CR + PR + SD[c])[b,d]						
Number of Patients (n, %)	13 (68.4)	13 (68.4)	16 (80.0)	16 (80.0)	89 (84.8)	91 (86.7)
95% Confidence Interval	(43.4, 87.4)	(43.4, 87.4)	(56.3, 94.3)	(56.3, 94.3)	(76.4, 91.0)	(78.6, 92.5)
Duration of Response (months)[e,f]						
Median (95% CI)	15.84 (12.0, NE)	15.08 (7.3, NE)	22.21 (12.0, NE)	0 (0.0)	20.86 (14.7, NE)	21.22 (17.7, 35.0)
Censored	5 (55.6)	5 (41.7)	5 (62.5)	0 (0.0)	31 (47.7)	32 (43.2)
Duration of Follow-Up (months)[e]						
Median	28.52	25.56	21.16	0 (0.0)	28.75	30.39
25th, 75th percentiles	14.7, 28.6	14.8, 26.7	17.5, 29.3	0 (0.0)	24.6, 31.3	26.7, 34.1
Rate (%) of Duration of Response[e,g]						
≥6 months (95% CI)	100.0 (NE, NE)	91.7 (53.9, 98.8)	100.0 (NE, NE)	0 (0.0)	87.7 (76.9, 93.6)	90.4 (81.0, 95.3)
≥12 months (95% CI)	100.0 (NE, NE)	58.3 (27.0, 80.1)	85.7 (33.4, 97.9)	0 (0.0)	72.2 (59.5, 81.5)	75.2 (63.5, 83.6)
≥24 months (95% CI)	37.5 (5.6, 71.7)	37.5 (10.9, 64.8).	35.7 (1.4, 78.0)	0	49.0 (36.1, 60.7)	46.9 (34.7, 58.1)
≥36 months (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0	43.4(30.0, 56.1)	26.6 (11.8, 44.0)

Eligible patients are treated on or before 15 December 2020. Stable disease includes Non-CR/Non-PD.

Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; N = number of patients; n = number of patients in specific category; NE = not estimable; NSCLC = non-small cell lung cancer; ORR = objective response rate; PR = partial response; RET = REarranged during Transfection; SD = stable disease.

a ORR is defined as the proportion of patients with best overall response of confirmed CR or PR. Response was confirmed by a repeat assessment ≥ 28 days.

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

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

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

e Estimate based on Kaplan-Meier method.

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

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

h First 105 Patients Enrolled with *RET* Fusion-Positive NSCLC Who Were Previously Treated with Platinum-Based Chemotherapy is a subset of patients with *RET* fusion-positive NSCLC previously treated with platinum-based chemotherapy.

Sources: Table 8.18, Table 8.19, Table 8.21, Table 8.22.

Time to response (TTR) and Time to best response (TBR)

Table 26: Time to Response Based on IRC and Investigator's Assessments Supportive Efficacy Analysis Sets

Status	Patients with *RET* Fusion-Positive NSCLC Previously Treated with Other Systemic Therapy (N=19)		Patients with Non-Measurable *RET* Fusion-Positive NSCLC (N=20)		First 105 Patients Enrolled with *RET* Fusion-Positive NSCLC Who Were Previously Treated with Platinum-Based Chemotherapy (N=105)	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
Time to Response (months)[a]						
Median	1.68	2.79	2.73		1.87	1.84
25th, 75th percentiles	1.6, 1.9	1.7, 3.7	1.7, 4.6		1.8, 3.7	1.7, 3.5
Min, max	0.7, 3.7	1.6, 22.0	0.9, 14.1		0.8, 13.7	0.7, 35.3
Time to Response, n (%)						
<2 months	7 (77.8)	6 (50.0)	4 (50.0)		41 (63.1)	53 (71.6)
≥2 to 4 months	2 (22.2)	4 (33.3)	2 (25.0)		11 (16.9)	15 (20.3)
≥4 to 6 months	0 (0.0)	0 (0.0)	1 (12.5)		6 (9.2)	3 (4.1)
≥6 to 9 months	0 (0.0)	1 (8.3)	0 (0.0)		2 (3.1)	0 (0.0)
≥9 months	0 (0.0)	1 (8.3)	1 (12.5)		5 (7.7)	3 (4.1)
Time to Best Response (months)[b]						
Median	1.68	2.79	2.73		1.87	1.84
25th, 75th percentiles	1.6, 1.9	1.7, 3.7	1.7, 4.6		1.8, 3.8	1.7, 3.5
Min, max	0.7, 3.7	1.6, 22.0	0.9, 14.1		0.8, 32.9	0.7, 35.3
Time to Best Response, n (%)						
<2 months	7 (77.8)	6 (50.0)	4 (50.0)		39 (60.0)	52 (70.3)
≥2 to 4 months	2 (22.2)	4 (33.3)	2 (25.0)		10 (15.4)	15 (20.3)
≥4 to 6 months	0 (0.0)	0 (0.0)	1 (12.5)		6 (9.2)	3 (4.1)
≥6 to 9 months	0 (0.0)	1 (8.3)	0 (0.0)		2 (3.1)	0 (0.0)
≥9 months	0 (0.0)	1 (8.3)	1 (12.5)		8 (12.3)	4 (5.4)

Progression-Free Survival

Table 27: Progression-Free Survival Based on IRC and Investigator Assessments Supportive Efficacy Analysis Sets

	Patients with *RET* Fusion-Positive NSCLC Previously Treated with Other Systemic Therapy (N=19)		Patients with Non-Measurable *RET* Fusion-Positive NSCLC (N=20)		First 105 Patients Enrolled with *RET* Fusion-Positive NSCLC Who Were Previously Treated with Platinum-Based Chemotherapy (N=105)	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
Progression Status, n (%)						
Disease progression	8 (42.1)	10 (52.6)	6 (30.0)	9 (45.0)	53 (50.5)	57 (54.3)
Died (no disease progression beforehand)	2 (10.5)	4 (21.1)	4 (20.0)	3 (15.0)	5 (4.8)	7 (6.7)
Censored	9 (47.4)	5 (26.3)	10 (50.0)	8 (40.0)	47 (44.8)	41 (39.0)
Duration of Progression-Free Survival (months)[a,b]						
Median	19.42	11.53	18.69	18.69	19.25	19.52
95% CI for median	3.5, 30.5	3.4, 30.5	9.1, NE	7.6, NE	13.9, 30.4	16.5, 28.6
Min, max	1.7+, 30.5	1.7, 30.5	3.0, 30.1+	3.0, 33.1+	0.3, 44.2+	0.0+, 44.2+
Duration of Follow-Up (months)[b]						
Median	30.26	30.26	22.08	24.87	30.32	33.08
25th, 75th percentiles	11.5, 30.4	21.4, 30.4	16.8, 24.9	19.4, 33.1	26.4, 35.6	28.7, 35.8
Rate (%) of Progression-free Survival[c]						
≥6 months (95% CI)	76.5 (48.8, 90.4)	63.2 (37.9, 80.4)	79.1 (53.2, 91.6)	80.0 (55.1, 92.0)	81.1 (71.9, 87.5)	82.1 (73.1, 88.3)
≥12 months (95% CI)	76.5 (48.8, 90.4)	47.4 (24.4, 67.3)	67.8 (41.7, 84.1)	69.3 (44.0, 84.9)	65.7 (55.5, 74.2)	68.1 (58.0, 76.2)
≥24 months (95% CI)	30.6 (8.0, 57.4)	30.1 (11.5, 51.3)	49.4 (24.8, 70.1)	37.3 (14.6, 60.4)	44.2 (34.0, 53.8)	41.8 (31.9, 51.4)
≥36 months (95% CI)	0.0 (NE, NE)	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)	37.5 (27.0, 47.9)	29.2 (18.0, 41.4)

Note: Status as of the patient's last disease assessment on or before 15 June 2021.
Abbreviations: CI = confidence interval; IRC = Independent Review Committee; max = maximum; min = minimum; N = number of patients; n = number of patients in specific category; NE = not estimable; NSCLC = non-small cell lung cancer; RET = REarranged during Transfection.
Sources: Table 8.25, Table 8.26.
[a] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[b] 95% CI was calculated using Brookmeyer and Crowley method.
[c] 95% CI was calculated using Greenwood's formula.

Overall Survival

Table 28: Overall Survival Supportive Efficacy Analysis Sets

Status	Patients with *RET* Fusion-Positive NSCLC Previously Treated with Other Systemic Therapy (N=19)	Patients with Non-Measurable *RET* Fusion-Positive NSCLC (N=20)	First 105 Patients Enrolled with *RET* Fusion-Positive NSCLC Who Were Previously Treated with Platinum-Based Chemotherapy (N=105)
Survival Status (n,%)[a]			
Dead	7 (36.8)	6 (30.0)	38 (36.2)
Censored	12 (63.2)	14 (70.0)	67 (63.8)
Reason Censored (n, %)			
Loss to Follow-up	1 (5.3)	0 (0.0)	0 (0.0)
OS Follow-up Ongoing	10 (52.6)	11 (55.0)	50 (47.6)
Withdrawal of Consent	1 (5.3)	3 (15.0)	17 (16.2)
Duration of Overall Survival (months)[b,c]			
Median	30.52	NE	NE
95% CI for median	11.0, NE	21.1, NE	33.5, NE
Min, max	2.3, 32.6+	3.0, 35.2+	0.3, 49.0+
Duration of Follow-up (months)[b]			
Median	26.18	22.77	33.05
25th, 75th percentiles	19.1, 31.6	19.1, 27.4	30.3, 37.1
Rate (%) of Overall Survival[b,d]			
≥12 months (95% CI)	72.7 (46.3, 87.6)	84.7 (59.7, 94.8)	88.2 (80.2, 93.2)
≥24 months (95% CI)	72.7 (46.3, 87.6)	71.9 (44.3, 87.5)	70.5 (60.4, 78.5)
≥36 months (95% CI)	NE (NE, NE	NE (NE, NE	59.2 (48.1, 68.7)

Abbreviations: CI = confidence interval; max = maximum; min = minimum; N = number of participants in the specified category; n = number of patients in specific category; NE = not estimable; NSCLC = non-small cell lung cancer; RET = REarranged during Transfection.

[a] Status as of the last contact on or before 15-JUN-2021.

[b] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.

CNS Response in the CNS Response Analysis Set

Measurable CNS disease

Table 29: CNS ORR and CNS DOR by IRC Assessments in RET Fusion-Positive NSCLC Patients with Measurable CNS Lesions- CNS Response Analysis Set

	NSCLC with Prior RT			No Prior Brain RT (N=16)	All NSCLC (N=26)
	Brain RT ≤2 Months Prior to First Dose (N=3)	Brain RT >2 Months Prior to First Dose (N=7)	All NSCLC with Prior RT (N=10)		
CNS Objective Response Rate[a] (CR + PR)					
Number of Patients with CR + PR (n, %)	3 (100.0)	5 (71.4)	8 (80.0)	14 (87.5)	22 (84.6)
95% CI[b]	(29.2, 100.0)	(29.0, 96.3)	(44.4, 97.5)	(61.7, 98.4)	(65.1, 95.6)
CNS Best Overall Response, n (%)					
Complete response	1 (33.3)	1 (14.3)	2 (20.0)	5 (31.3)	7 (26.9)
Partial response	2 (66.7)	4 (57.1)	6 (60.0)	9 (56.3)	15 (57.7)
Stable disease	0 (0.0)	2 (28.6)	2 (20.0)	2 (12.5)	4 (15.4)
SD[c]	0 (0.0)	2 (28.6)	2 (20.0)	0 (0.0)	2 (7.7)
Progressive disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Undefined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CNS Clinical Benefit Rate					
Number of Patients with CR + PR + SD[c] (n, %)	3 (100.0)	7 (100.0)	10 (100.0)	14 (87.5)	24 (92.3)
95% CI[b]	(29.2, 100.0)	(59.0, 100.0)	(69.2, 100.0)	(61.7, 98.4)	(74.9, 99.1)
CNS Duration of Response (months)[d,e]					
No. of patients censored, n (%)	1 (33.3)	2 (40.0)	3 (37.5)	3 (21.4)	6 (27.3)
Median (95% CI)	8.28 (5.1, 8.3)	12.12 (3.7, NE)	8.28 (3.7, NE)	9.36 (6.7, 15.3)	9.36 (7.4, 15.3)
Minimum, Maximum	5.1, 8.3	3.7, 25.8+	3.7, 25.8+	2.8, 35.0+	2.8, 35.0+
CNS Duration of Response Follow-up (months)[d]					
Median	NR	24.84	23.89	26.68	25.79
25^{th}, 75^{th} Percentiles	7.4, NE	23.9, 25.8	23.9, 25.8	26.7, 35.0	23.9, 26.7
CNS Rate (%) of Duration of Response[d,f]					
≥6 months (95% CI)	66.7 (5.4, 94.5)	80.0 (20.4, 96.9)	75.0 (31.5, 93.1)	85.7 (53.9, 96.2)	81.8 (58.5, 92.8)
≥12 months (95% CI)	0.0 (NE, NE)	60.0 (12.6, 88.2)	45.0 (10.8, 75.1)	31.2 (9.7, 55.9)	36.1 (16.4, 56.4)
≥24 months (95% CI)	0.0 (NE, NE)	40.0 (5.2, 75.3)	30.0 (4.4, 62.8)	15.6 (2.5, 39.1)	20.6 (6.5, 40.2)
≥36 months (95% CI)	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Note: + = censored observation.

Note: Partial response is not applicable for non-measurable patients. Stable disease includes non-CR/non-PD.

Abbreviations: CI = confidence interval; CNS = central nervous system; CR = complete response; DOR = duration of response; IRC = Independent Review Committee; N = number of patients; n = number of patients in specific category; NE = not estimable; No. = number; NR = not reported; NSCLC = non-small cell lung cancer; ORR = objective response rate; PR = partial response; RT = radiation therapy.

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

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

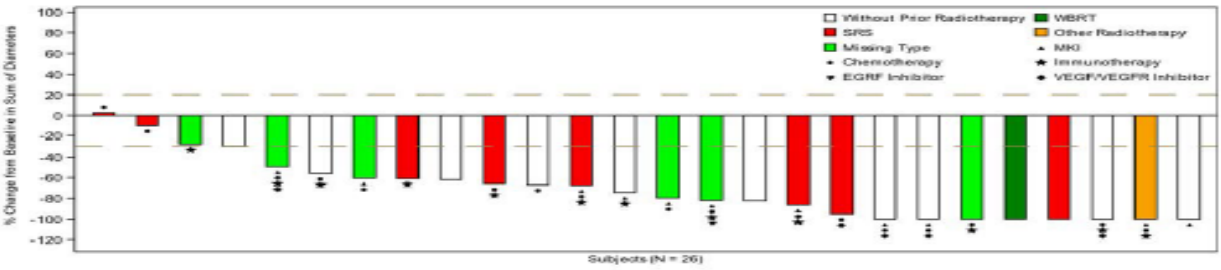
c Indicates SD lasting ≥ 16 weeks following initiation of selpercatinib until the criteria for disease progression was first met.

d Estimate based on Kaplan-Meier method. NE = Not estimable. NR = Not reached. + = Censored observation.

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

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

Figure 15. Waterfall plot of best change in CNS tumour burden by prior therapy based on IRC assessments in patients with measurable CNS disease-CNS response analysis set



'SRS' includes all patients reported to receive SRT, SBRT, GKS, and/or SRS. 'WBRT' includes all patients reported to receive radiation of any kind to the 'whole brain' including conventional external beam, IMRT, and 3DCRT.
For each subject, the best percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar. The dashed lines represent the RECIST v1.1. criteria for response (30% decrease) or progressive disease (20% increase).
Abbreviations: CNS = central nervous system; DCRT = definitive chemoradiotherapy; EGFR = epidermal growth factor receptor; GKS = gamma knife surgery; IMRT = intensity modulated radiotherapy; MKI = multikinase inhibitor; RECIST = Response Evaluation Criteria in Solid Tumors; SBRT = stereotactic body radiotherapy; SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; WBRT = whole brain radiotherapy.

Non-measurable CNS disease

The CNS ORR in the 80 patients with RET fusion-positive NSCLC and non-measurable CNS metastasis at baseline was 37.5% (95% CI: 26.9, 49.0), by IRC. The CNS CBR was 75.0% (95% CI: 64.1, 84.0) by IRC.

The median CNS DOR by IRC for patients with CNS non-measurable disease was not yet reached (95% CI: 22.1, NE) at a median follow-up time of 20.70 months.

CNS Response in Treatment-Naïve Patients with RET Fusion-Positive NSCLC

Measurable CNS Disease

Table 30. CNS ORR and CNS DOR by IRC Assessments – RET Fusion-Positive Treatment-Naïve Patients with Measurable CNS Lesions CNS Response Analysis Set

	NSCLC with Prior RT			No Prior Brain RT (N=3)	All NSCLC (N=5)
	Brain RT ≤2 Months Prior to First Dose (N=2)	Brain RT >2 Months Prior to First Dose (N=0)	All NSCLC with Prior RT (N=2)		
CNS Objective Response Rate[a] (CR + PR)					
Number of Patients with CR + PR (n, %)	2 (100.0)	NA	2 (100.0)	2 (66.7)	4 (80.0)
95% CI[b]	(15.8, 100.0)	NA	(15.8, 100.0)	(9.4, 99.2)	(28.4, 99.5)
CNS Best Overall Response, n (%)					
Complete response	1 (50.0)	NA	1 (50.0)	0 (0.0)	1 (20.0)
Partial response	1 (50.0)	NA	1 (50.0)	2 (66.7)	3 (60.0)
Stable disease	0	NA	0 (0.0)	1 (33.3)	1 (20.0)
SD[c]	0	NA	0 (0.0)	0 (0.0)	0 (0.0)
Progressive disease	0	NA	0 (0.0)	0 (0.0)	0 (0.0)
Not evaluable	0	NA	0 (0.0)	0 (0.0)	0 (0.0)
Undefined	0	NA	0 (0.0)	0 (0.0)	0 (0.0)
CNS Clinical Benefit Rate					
Number of Patients with CR + PR + SD[c] (n, %)	2 (100.0)	NA	2 (100.0)	2 (66.7)	4 (80.0)
95% CI[b]	(15.8, 100.0)	NA	(15.8, 100.0)	(9.4, 99.2)	(28.4, 99.5)
CNS Duration of Response (months)[d,e]					
No. of patients censored, n (%)	1 (50.0)	NA	1 (50.0)	0	1 (25.0)
Median (95% CI)	NR (5.1, NE)	NA	NR (5.1, NE)	12.19 (9.0, 15.3)	9.03 (5.1, 15.3)
Minimum, Maximum	5.1, 7.4+	NA	5.1, 7.4+	9.0, 15.3	5.1, 15.3
CNS Duration of Response Follow-up (months)[d]					
Median	7.39	NA	7.39	NR	NR
25th, 75th Percentiles	7.4, 7.4	NA	7.4, 7.4	NE, NE	7.4, NE
CNS Rate (%) of Duration of Response[d,f]					
≥6 months (95% CI)	50.0 (0.6, 91.0)	NA	50.0 (0.6, 91.0)	100.0 (NE, NE)	75.0 (12.8, 96.1)
≥12 months (95% CI)	NE (NE, NE)	NA	NE (NE, NE)	50.0 (0.6, 91.0)	37.5 (1.1, 80.8)
≥24 months (95% CI)	0.0 (NE, NE)	NA	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
≥36 months (95% CI)	0.0 (NE, NE)	NA	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Note: + = censored observation.

Note: Partial response is not applicable for non-measurable patients. Stable disease includes non-CR/PD.

Abbreviations: CI = confidence interval; CNS = central nervous system; CR = complete response; DOR = duration of response; IRC = Independent Review Committee; N = number of patients; n = number of patients in specific category; NE = not estimable; No. = number; NR = not reported; NSCLC = non-small cell lung cancer; ORR = objective response rate; PR = partial response; RET = REarranged during Transfection; RT = radiation therapy.

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

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

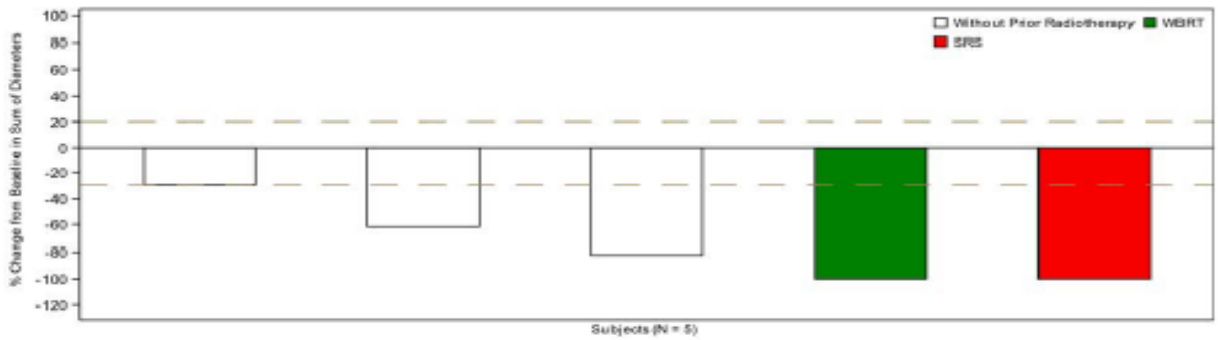
c Indicates SD lasting ≥ 16 weeks following initiation of selpercatinib until the criteria for disease progression was first met.

d Estimate based on Kaplan-Meier method. NE = Not estimable. NR = Not reached. + = Censored observation.

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

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

Figure 16. Waterfall plot of best change in CNS tumour Burden by Prior therapy based on IRC assessments in treatment-naïve patients-CNS response analysis set



Note: The dashed lines represent the RECIST v1.1. criteria for response (30% decrease) or progressive disease (20% increase).
Abbreviations: CNS = central nervous system; IRC = Independent Review Committee; N = number of patients; RECIST = Response Evaluation Criteria in Solid Tumors; SRS = stereotactic radiosurgery ; WBRT = whole brain radiotherapy.

Non-Measurable CNS Disease

The CNS ORR in the 11 patients with RET fusion-positive treatment-naïve and CNS metastasis with non-measurable CNS disease at baseline was 27.3% (95% CI: 6.0, 61.0) by IRC.

The median CNS DOR for treatment-naïve patients with CNS non-measurable disease was not yet reached (95% CI: NE, NE) at a median follow-up time of 21.0 months.

Median duration of observed PFS in patients with RET fusion-positive treatment-naïve NSCLC and non-measurable CNS metastasis (N=11) was not estimable (95% CI: 3.7, NE) with a median duration of follow-up of 21.9 months.

CNS Response in Patients with RET Fusion-Positive NSCLC Previously Treated with Platinum-Based Chemotherapy

Measurable CNS Disease

Table 31. CNS ORR and CNS DOR by IRC Assessments RET Fusion-Positive NSCLC Previously Treated with Platinum-Based Chemotherapy Patients with Measurable CNS Lesions-CNS Response Analysis Set

	NSCLC with Prior RT			No Prior Brain RT (N=9)	All NSCLC (N=16)
	Brain RT ≤2 Months Prior to First Dose (N=1)	Brain RT >2 Months Prior to First Dose (N=6)	All NSCLC with Prior RT (N=7)		
CNS Objective Response Rate[a] (CR + PR)					
Number of Patients with CR + PR (n, %)	1 (100.0)	4 (66.7)	5 (71.4)	9 (100.0)	14 (87.5)
95% CI[b]	(2.5, 100.0)	(22.3, 95.7)	(29.0, 96.3)	(66.4, 100.0)	(61.7, 98.4)
CNS Best Overall Response, n (%)					
Complete response	0 (0.0)	1 (16.7)	1 (14.3)	4 (44.4)	5 (31.3)
Partial response	1 (100.0)	3 (50.0)	4 (57.1)	5 (55.6)	9 (56.3)
Stable disease	0 (0.0)	2 (33.3)	2 (28.6)	0 (0.0)	2 (12.5)
SD[c]	0 (0.0)	2 (33.3)	2 (28.6)	0 (0.0)	2 (12.5)
Progressive disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Undefined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CNS Clinical Benefit Rate					
Number of Patients with CR + PR + SD[c] (n, %)	1 (100.0)	6 (100.0)	7 (100.0)	9 (100.0)	16 (100.0)
95% CI[b]	(2.5, 100.0)	(54.1, 100.0)	(59.0, 100.0)	(66.4, 100.0)	(79.4, 100.0)
CNS Duration of Response (months)[d,e]					
No. of patients censored, n (%)	0 (0.0)	2 (50.0)	2 (40.0)	3 (33.3)	5 (35.7)
Median (95% CI)	8.28 (NE, NE)	NR (7.4, NE)	12.12 (7.4, NE)	10.05 (5.4, NE)	10.05 (7.4, NE)
Minimum, Maximum	8.3, 8.3	7.4, 25.8+	7.4, 25.8+	5.4, 35.0+	5.4, 35.0+
CNS Duration of Response Follow-up (months)[d]					
Median	NR	24.84	24.84	26.68	25.79
25th, 75th Percentiles	NE, NE	23.9, 25.8	23.9, 25.8	26.7, 35.0	23.9, 26.7
CNS Rate (%) of Duration of Response[d,f]					
≥6 months (95% CI)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)	88.9 (43.3, 98.4)	92.9 (59.1, 99.0)
≥12 months (95% CI)	0.0 (NE, NE)	75.0 (12.8, 96.1)	60.0 (12.6, 88.2)	25.4 (3.8, 56.4)	38.7 (14.2, 63.0)
≥24 months (95% CI)	0.0 (NE, NE)	50.0 (5.8, 84.5)	40.0 (5.2, 75.3)	25.4 (3.8, 56.4)	31.0 (9.6, 55.6)
≥36 months (95% CI)	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Note: + = censored observation.

Note: Partial response is not applicable for non-measurable patients Stable disease includes non-CR/PD.

Abbreviations: CI = confidence interval; CNS = central nervous system; CR = complete response; DOR = duration of response; IRC = Independent Review Committee; N = number of patients; n = number of patients in specific category; NE = not estimable; NR = not reported; NSCLC = non-small cell lung cancer; ORR = objective response rate; PR = partial response; RT = radiation therapy.

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

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

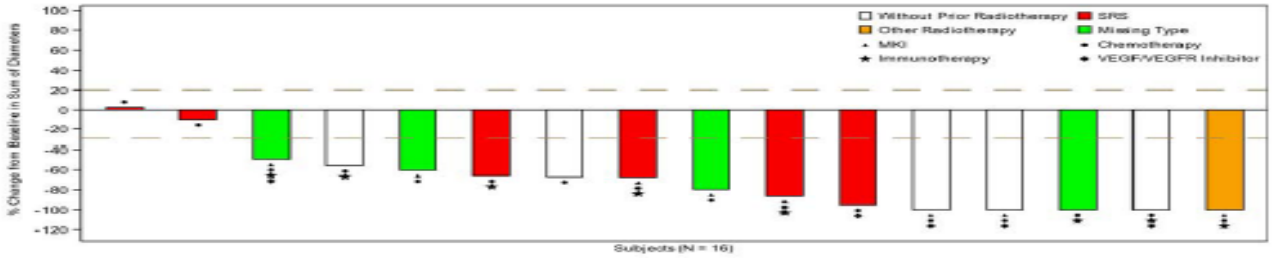
c Indicates SD lasting ≥ 16 weeks following initiation of selpercatinib until the criteria for disease progression was first met.

d Estimate based on Kaplan-Meier method. NE = Not estimable. NR = Not reached. + = Censored observation.

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

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

Figure 17. Waterfall plot of best change in CNS tumour burden by prior therapy based on IRC assessments in RET fusion-positive NSCLC patients previously treated with platinum-based chemotherapy - CNS response analysis set



Eligible patients are defined as patients treated on or before 15 December 2020.
'SRS' includes all patients reported to receive SRT, SBRT, GKS and/or SRS. 'WBRT' includes all patients reported to receive radiation of any kind to the 'whole brain', including conventional external beam, IMRT and 3DCRT.
For each subject, the best percent change from baseline in the sum of diameters for all target CNS lesions is represented by a vertical bar. The dashed lines represent the RECIST v1.1. criteria for response (30% decrease) or progressive disease (20% increase).
Abbreviations: CNS = central nervous system; DCRT = definitive chemoradiotherapy; EGFR = epidermal growth factor receptor; GKS = gamma knife surgery; IMRT = intensity modulated radiotherapy; MKI = multikinase inhibitor; RECIST = Response Evaluation Criteria in Solid Tumors; RET = REarranged during Transfection; SBRT = stereotactic body radiotherapy; SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; WBRT = whole brain radiotherapy.

Non-Measurable CNS Disease

The CNS ORR in the 61 patients with RET fusion-positive NSCLC previously treated with platinum therapy and CNS metastasis with non-measurable CNS disease at baseline was 39.3% (95% CI: 27.1, 52.7), by IRC.

The median CNS DOR for patients with CNS measurable disease was not yet reached (95% CI: 12.1, NE) at a median follow-up time of 20.3 months.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32. Summary of Efficacy for trial LIBRETTO-001

Title: A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumours, Including RET Fusion-Positive Solid Tumours, Medullary Thyroid Cancer and Other Tumours with RET Activation (LIBRETTO-001)			
Study identifier	LOXO-RET-17001; LIBRETTO-001		
Design	Phase 1/2, multicentre, open-label		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		ongoing not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Selpercatinib		Oral 10-, 20- or 80- mg capsules or 20 mg/mL suspension, QD or BID Dose escalation: 20 mg QD to 240 mg BID. Phase 2: 160mg BID
Endpoints and definitions	Primary endpoint	Objective response rate (ORR) by IRC	Proportion of patients with best overall response of confirmed complete response (CR) or confirmed partial response (PR) based on RECIST, 1.1.

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

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	**RET Fusion-Positive NSCLC Patients- Treatment-Naïve** DCO: 15 June 2021	
Descriptive statistics and estimate variability	Treatment group	Selpercatinib
	Number of patients	69
	ORR % (95% CI) by IRC	58 (84.1) (73.3, 91.8)
	DOR median, months (95% CI) by IRC	20.21 (13.0, NE)
	PFS median, months (95% CI) by IRC	21.95 (13.8, NE)
	OS landmark rates (%) (95% CI)	92.7 at 12 months (83.3, 96.9) 69.3 at 24 months (55.2, 79.7) 57.1 at 36 months (35.9, 73.6)
Analysis population and time point description	**RET-Fusion Positive NSCLC-Prior Platinum Chemotherapy** DCO: 15 June 2021	
Descriptive statistics and estimate variability	Treatment group	Selpercatinib
	Number of patients	247
	ORR % (95% CI)	151 (61.1) (54.7, 67.2)
	DOR median, months (95% CI)	28.58 (20.4, NE)
	PFS median, months (95% CI)	24.94 (19.3, NE)
	OS landmark rates (%) (95% CI)	87.9 at 12 months (83.0, 91.4) 68.9 at 24 months (62.2, 74.7) 58.5 at 36 months (49.7, 66.3)
Effect estimate per comparison	Not applicable, single arm trial	
Notes	CI = confidence interval; NE = not estimable	

Clinical studies in special populations

No data from clinical studies in special populations was submitted in this application.

In the table below, the number of elderly patients included in the LIBRETTO-001 trial is presented.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
LIBRETTO-001 trial RET Fusion-Positive NSCLC Patients-Treatment-Naïve	24/69 (34.8%)	4/69 (5.8%)	3/69 (4.3%)

2.4.3. Discussion on clinical efficacy

The MAH is seeking by this application an extension of indication of selpercatinib for the first line treatment of advanced RET fusion-positive NSCLC. Selpercatinib has a conditional approval for previously treated advanced RET fusion-positive NSCLC (immunotherapy and/or platinum based chemotherapy). In addition, a CMA was granted to thyroid cancer patients following prior treatment with sorafenib and/or lenvatinib and advanced RET mutant medullary thyroid cancer (MTC) following prior treatment with cabozantinib and/or vandetanib. In order to fulfil this CMA, clinical data are to be provided as a SOB from two separate ongoing phase 3 studies within a specified timeframe (Annex II of the SmPC); J2G-MC-JZJC (LIBRETTO-431) in treatment-naive RET-fusion non-squamous NSCLC and J2G-MC-JZJB (LIBRETTO-531) in previously untreated RET-mutant MTC.

The provided efficacy data in support of the currently intended indication "advanced RET fusion positive NSCLC" is based on results from the ongoing study LOXO-RET-17001 (LIBRETTO-001) as of the cut-off date of 21 June 2021. This was an open-label, multicentre, Phase 1/2 study which consisted on a dose escalation phase (Phase 1) to determine the MTD and RP2D of selpercatinib followed by a Phase 2 expansion with diverse RET-altered cancer cohorts (6 cohorts), among them NSCLC (1L/2L), MTC, and other tumours.

The Phase 1 portion of the study has been completed. The Phase 2 portion is ongoing and continuing to enroll patients with advanced solid tumours. The study was however closed for enrollment of patients with RET fusion-positive NSCLC in May 2020.

Design and conduct of clinical study

LIBRETTO-001 is non-randomized and non-blinded single arm study. The absence of a control arm is an important limitation and a source of bias for a confirmatory study. Overall, inclusion and exclusion criteria are considered acceptable. Amendments made on eligibility criteria since the initial submission of the CMA (DCO of June 2019) are not expected to have a substantial impact on study population or efficacy data. A new cohort, cohort 6, was introduced by amendment protocol (version 9) to include patients who discontinued another selective RET inhibitor because of intolerance. Efficacy data from patients with NSCLC in this cohort is not yet available and this was adequately reflected in the therapeutic indication.

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

The primary efficacy endpoint was ORR based on RECIST v1.1. Given the uncontrolled design of the clinical trial, ORR could be an acceptable primary endpoint. PFS, OS and DOR were assessed as secondary endpoints. CNS ORR and DOR were also included as secondary endpoints. It is important to consider

that even if results in term of ORR are outstanding, interpretation of benefit in term of survival endpoints is difficult and uncertain in uncontrolled setting.

Some non-substantial modifications are made to the SAP as outlined in the SAP addendum 1 dated 14 June 2021. There is no change to efficacy analysis sets defined in the original version of the SAP. FDA censoring rules were used for DoR and PFS.

Up to DCO of 15 June 2021, 921 patients were screened. Of these, 123 patients have failed screening (13.4%), with main reason not satisfying all inclusion and exclusion criteria. 796 patients had been enrolled in the Phase 1 and Phase 2 cohorts and were treated with at least 1 dose of selpercatinib. Of these, 356 patients had RET fusion-positive NSCLC. All these patients fulfilled the efficacy dataset requirement to allow for appropriate response assessment (at least 6 months of a potential follow-up time). One patient from cohort 6 received prior treatment with a selective RET inhibitor and therefore is not included in the efficacy analysis. Of the 355 patients with RET fusion-positive NSCLC, 69 patients were treatment-naïve and 247 patients were previously treated with platinum based chemotherapy. Of note, this corresponds to enrolment of 21 additional treatment-naïve patients and 29 additional previously treated patients from 30 March 2020 to 15 June 2021.

Of the 355 patients with RET fusion-positive NSCLC, 165 (46.5%) patients were still on treatment. Of the 69 treatment-naïve patients, 46.4% of patients were still on treatment and the main reason for treatment discontinuation was disease progression (37.7%) followed by AEs (8.7%). Of the 247 patients who were previously treated, 47.4% of patients were still on treatment and the main reason for treatment discontinuation was disease progression (29.6%) followed by AEs (9.3%).

The MAH provides information on study conduct from Protocol version 8.0 up to Protocol version 9.0 (03 June 2020). Some of the changes introduced with Protocol v8 are the addition of the new cohort 6 to allow the inclusion of patients previously treated with another RET-selective inhibitor with around 50 patients planned to be enrolled. Moreover, with protocol v9 the number of patients to be enrolled in Cohort 1 is increased to 250 participants and Cohort 5 up to approximately 200 in order to accommodate enrollment demand of patients with RET fusion-positive solid tumours other than NSCLC and to allow for the characterization of AEs that may occur with low frequency.

Regarding protocol deviations, 25.8% of NSCLC patients had at least one major protocol deviation.

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

Treatment-Naïve Patients had a median age of 63 years (range: 23-92), being 10% 75 years or older. 62.3% of patients were female, 69.6% were White and 18.8% Asian. The majority of patients had an ECOG PS of 0 (36.2%) or 1 (58%) and had never smoked (69.6%) or were former smokers (27.5%). History of metastatic disease was present in 98.6% and 23.2% of patients had CNS metastases at baseline. The median time from initial diagnosis and diagnosis of metastatic disease were 2.0 and 1.6 months, respectively. 98.6% had metastases and 1.4% had advanced disease at enrollment as reported by the Investigator.

The most common fusion partners were KIF5B (70%) and CCDC6 (14.5%). Moreover, there were 8 patients (11.6%) in which fusion partner was unknown. In the majority of cases, the RET alteration was determined by NGS, 60.9% on tumour and 30.4% on plasma/blood.

Efficacy data and additional analyses

The evidence supporting of the claimed indication in first line NSCLC came from the 69 treatment naïve patients which could be considered limited to generate evidence. Supportive evidence came mostly from

the 247 patients previously treated (Platinum-Based Chemotherapy) and the 26 evaluable patients who had CNS measurable disease by IRC.

Treatment-naïve advanced NSCLC

As of the cut-off date of 21 June 2021, the ORR among 69 treatment-naïve patients was 84.1% (95% CI: 73.3, 91.8) by IRC and 85.5% (95% CI: 75.0, 92.8) by Investigator (Inv). Concordance between the IRC and Investigator assessments is 89.9% (95% CI: 80.2, 95.8).

The median DOR by IRC was 20.2 months (95% CI: 13.0, NE) with 39.7% of patients continuing treatment or PD free at median follow-up of 21.2 months. The mDOR by inv was 20.27 months (14.8; NE). Kaplan-Meier estimates of the rate of duration of response at 12 months was 66.1% (95% CI: 51.6, 77.3) and at 24 months was 41.6% (95% CI: 25.6, 56.8). A stable median cannot yet be estimated.

The median TTR by IRC was 1.81 months, with most patients demonstrating an initial and best response at the first post-baseline radiographic assessment.

Median duration of observed PFS by IRC was 21.95 months (95% CI: 13.8, NE) with 53.6% of the patients remaining progression free with a median follow-up of 21.91 months. mPFS by inv is 20.73 months (13.6, NE). PFS data is not yet considered mature. KM estimates of the rate of PFS by IRC at 12 months or more was 70.6% (95% CI: 57.8, 80.2), and at 24 months was 41.6% (95% CI: 26.8, 55.8).

Sensitivity analyses for PFS and DOR where patients who received a subsequent anti-cancer therapy are imputed as event were provided and results were consistent with the main analyses.

Median duration of observed OS was not estimable with 71.0% patients remaining alive at a median follow-up of 25.2 months. The rate of OS at 24 months was 69.3%, and at 36 months was 57.1%.

Analysis by subgroups in the treatment naïve patient's population did not reveal any remarkable difference to main analysis. Overall, ORR were mostly in line with the main analysis.

Prior-platinum treated advanced NSCLC

The ORR in the 247 patients previously treated with platinum-based chemotherapy (previously named IAS) was of 61.1% (95% CI: 54.7, 67.2) by IRC and 64.4% (95% CI: 58.1, 70.3) by Inv with a concordance rate of 74.9% (69.0, 80.2). There were 133 PRs (53.8%) and 18 CRs (7.3%).

The median TTR by IRC was 1.87 months. Estimated mPFS by IRC was 24.94 months (95% CI: 19.3, NE) with a median follow-up of 24.71 months. mPFS by inv was 21.75 months (95% CI: 16.8, 24.9). Due to the number of patients who were progression free (55.9%), the PFS data is not yet mature. KM estimates of the rate of PFS by IRC at 12 months was 70.5% (95% CI: 64.1, 76.0) and at 24 months was 51.4% (95% CI: 44.3, 58.1).

The median DOR by IRC was 28.6 months (95% CI: 20.4, NE) with 49.0% of patients continuing treatment or PD free at median follow-up of 21.2 months. The mDOR by inv was slightly lower (21.22 months (95% CI: 18.4, 31.8). This could be explained by the fact that the data are still not mature, with censoring rates of 50.3% (investigator assessed) and 60.9% (IRC-assessed).

Median duration of OS was not estimable with 57.9% of the patients remaining alive and continuing OS follow-up at a median follow-up time of 26.4 months. The rate of OS at 24 months was 68.9%, and at 36 months was 58.5%.

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

ORR remained consistent across the pre-specified subgroups except for subgroups of the RET fusion partner genes where the ORR for patients with CCDC6-RET (81.1%; 95% CI, 68.0, 90.6) was higher compared to those with KIF5B-RET fusion (55.6%; 95% CI, 47.3, 63.6). Response appears to be lower

in those patients with non-KIF5B/non-CCDC6 fusion (47.6%) although the number of patients is low (n=21). Although these results cannot be readily attributed to a specific covariate(s) or identified mechanistic differences in the underlying biology, the ORRs observed in the NSCLC population with KIF5B (55.6%; n=153), CCDC6 (81.1%; n=53), and non-KIF5B/CCDC6 (47.6%; n=21) exceed those observed with standard chemotherapy (8.8% to 23%) or monotherapy immune checkpoint inhibitors (13.7% to 33.1%). The confirmatory Phase 3 study, LIBRETTO-431, will provide an opportunity to obtain more data on the efficacy of selpercatinib with different fusion partners, data on the predictive and prognostic value of different fusion partners, and inform whether this result is potentially attributable to underlying biology or is unique to the LIBRETTO-001 dataset.

The ORR benefit of selpercatinib for the intended population was observed regardless of line of treatment. But, higher ORR in the treatment-naïve population (81%) were observed and this subpopulation has a lower K-M estimates of median PFS (21.95 months) and mDOR (20.2 months) compared to the prior-platinum subpopulation (24.94 months and 28.6 months, respectively). The MAH clarified that this is likely a result of the random statistical variability that comes from comparing point estimates in a small dataset that is not yet mature.

CNS responses

CNS metastasis are common in lung cancer patients. Of the 355 patients with NSCLC, 106 patients had CNS metastasis at baseline by Inv, of whom 26 had CNS measurable disease by IRC. ORR in the 26 patients with measurable CNS metastasis was 84.6% (95% CI: 65.1, 95.6), including 7 CRs (27%) and 15 PRs (58%) with a median duration of response of 9.36 months (95% CI: 7.4, 15.3). Median PFS by IRC for these patients (N=26) was 11.01 months (95% CI: 9.2, 17.1).

ORR was much lower in the total 80 patients with non-measurable CNS metastasis at baseline with ORR of 37.5% (95% CI: 26.9, 49.0), by IRC. Per RECIST 1.1, in a non-measurable population, only patients achieving a CR are considered to be responders. The median CNS DOR by IRC for these patients was not yet reached (95% CI: 22.1, NE) at a median follow-up time of 20.70 months.

Responses were observed both in patients previously treated with platinum based chemotherapy as well as treatment-naïve patients.

Other supportive analyses

In patients with RET fusion-positive NSCLC previously treated with other systemic therapy (N=19), ORR by IRC was 47.4% (95% CI: 24.4, 71.1), the mDOR was 15.84 months with median duration of follow-up of 28.52 months. mPFS by IRC was 19.42 months (95% CI: 3.5, 30.5) with a median follow up of 30.26 months.

Among Patients with non-measurable RET fusion-positive NSCLC by inv (N=20), 8 patients were deemed to have measurable disease by the IRC. The ORR by IRC was 40.0% (95% CI: 19.1, 63.9). mDOR by IRC was 22.21 with median duration of follow-up of 21.16 months. mPFS by IRC was 18.69 months (95% CI: 9.1, NE) with a median follow-up of 22.08 months.

In the first enrolled 105 previously treated patients, who have the longest potential follow-up time, ORR by IRC was 61.9% (95% CI: 51.9, 71.2). mDOR was 20.86 months with median duration of follow-up of 28.75 months. mPFS by IRC was 19.25 (95% CI: 13.9, 30.4) with a median follow up of 30.32 months.

2.4.4. Conclusions on the clinical efficacy

The updated efficacy results from the ongoing phase 1/2 study LIBRETTO-001 in previously treated NSCLC are consistent with those provided in the original submission. For treatment naïve patients, the obtained ORR of 84% is considered clinically meaningful. Responses seem durable and K-M estimates

for median PFS and OS allow to anticipate lasting benefits from treatment. Selpercatinib has shown activity in patients with CNS disease regardless of line of therapy.

Although, other approved front-line therapies with established benefit exist, efficacy with selpercatinib is considered of sufficient magnitude and across multiple lines of therapy. Since efficacy results are based on a single clinical trial with a low number of treatment-naïve subjects (n=69), data corresponding to a longer follow-up are still required as well as efficacy results from the ongoing phase 3 study LIBRETTO-431 (the SOB study related to the CMA).

2.5. Clinical safety

Introduction

Safety data are available from a total of 796 patients in the LIBRETTO 001 study which is still ongoing. All patients in the ITT population received at least one dose of selpercatinib as of the data cutoff date of 15 June 2021.

Table 33. Description of Safety Analysis Sets (Data Cutoff Date: 15 June 2021)

Safety Analysis	Analysis Set Description
Overall Safety Population (N=796)	All patients who received at least 1 dose of selpercatinib, including: • *RET* fusion-positive NSCLC • *RET* fusion-positive thyroid cancer • *RET*-mutant MTC • *RET*-altered other cancers, and • Other cancers without a *RET* alteration[a]
Treatment-Naïve Safety Population (N=69)	All treatment-naïve patients with *RET* fusion-positive NSCLC who received at least 1 dose of selpercatinib. This is a subset of the Overall Safety Population.
NSCLC Safety Population (n=356)	All patients with documented *RET* fusion-positive NSCLC who received at least 1 dose of selpercatinib. This is a subset of the Overall Safety Population.
Previously Treated with Platinum-Based Chemotherapy Safety Population (N=248)	All patients with *RET* fusion-positive NSCLC previously treated with platinum-based chemotherapy who received at least 1 dose of selpercatinib. This is a subset of the Overall Safety Population.

Abbreviations: MTC = medullary thyroid cancer; N = number of patients; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; RET = rearranged during transfection.

[a] Note that during Phase 1, a *RET* gene alteration was not required for enrolment until adequate PK exposure was achieved.

Patient exposure

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

Five hundred thirty-nine (539) patients (68%) were still on study, of which 462 patients (58%) were still receiving selpercatinib and 77 patients (10%) were in follow-up, but off treatment.

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

In the NSCLC Safety Population, 95.8% patients received at least 1 dose of selpercatinib 160 mg BID and 87.4% patients had a selpercatinib starting dose of 160 mg.

Table 34. Treatment and study disposition (NSCLC Safety Population)

Status	Integrated (N=248)	SAS1 (N= 69)	RET Fusion-positive NSCLC (N=356)
Treatment Status (n, %)			
Discontinued	130 (52.4)	37 (53.6)	190 (53.4)
Continuing	118 (47.6)	32 (46.4)	166 (46.6)
Reason Treatment Discontinued (n, %)			
Progressive Disease	73 (29.4)	26 (37.7)	115 (32.3)
Adverse Event	23 (9.3)	6 (8.7)	32 (9.0)
Intercurrent Illness Compromising Ability to Fulfill Protocol Requirements	1 (0.4)	0 (0.0)	1 (0.3)
Requirement for Alternative Treatment per Investigator	2 (0.8)	0 (0.0)	2 (0.6)
Withdrawal of Consent	14 (5.6)	3 (4.3)	17 (4.8)
Death	8 (3.2)	2 (2.9)	14 (3.9)
Other	9 (3.6)	0 (0.0)	9 (2.5)
Study Status (n, %)			
Discontinued	104 (41.9)	25 (36.2)	147 (41.3)
Continuing	144 (58.1)	44 (63.8)	209 (58.7)
Reason Study Discontinued (n, %)			
Withdrawal of Consent	25 (10.1)	5 (7.2)	34 (9.6)
Lost to Follow-Up	1 (0.4)	0 (0.0)	2 (0.6)
Death	78 (31.5)	20 (29.0)	111 (31.2)

The median time on treatment was 21.29 and 19.09 months, respectively, for the Overall Safety Population and NSCLC Safety Population.

The most reported dose modification was dose withheld (72.9% in the Overall Safety Population and 77.5% in the NSCLC Safety Population) primarily attributed to adverse events (AEs) (64.1% in the Overall Safety Population and 68.8% in the NSCLC Safety Population).

Adverse events

A summary of all-causality and treatment-related AEs registered by data-cutoff is shown in below table

Table 35. Summary of Safety Trends- Overall Safety Population

Data Cut-Off Date	16 December 2019	30 March 2020	15 June 2021
Patients with	N=702	N=746	N=796
any TEAE, n (%)	695 (99.0)	740 (99.2)	**795 (99.9)**
Related to selpercatinib	640 (91.2)	690 (92.5)	**756 (95.0)**
Grade ≥3 TEAEs, n (%)	415 (59.1)	445 (59.7)	**572 (71.9)**
Related to selpercatinib	206 (29.3)	239 (32.0)	**307 (38.6)**
TEAEs leading to treatment discontinuation, n (%)	37 (5.3)	45 (6.0)	**64 (8.0)**
Related to selpercatinib	14 (2.0)	16 (2.1)	**25 (3.1)**
TESAEs, n (%)	234 (33.3)	262 (35.1)	**353 (44.3)**
Related to selpercatinib	54 (7.7)	62 (8.3)	**87 (10.9)**
fatal TEAEs, n (%)	21 (3.0)	25 (3.4)	**45 (5.7)**
Related to selpercatinib	0	0	**1 (0.1)**

Table 36. Adverse Drug Reactions in LIBRETTO-001-Overall Safety Population

System Organ Class	Event	Selpercatinib (N=796)		
		Any Grades Toxicity (%)	Grade 3 Toxicity (%)	Grade 4 Toxicity (%)
Immune system disorders[a]	*Hypersensitivity*[b]	5.9	1.9	0
Metabolism and nutrition disorders	Decreased appetite	18.8	0.4	0
Nervous system disorders	*Headache*[b]	27.6	1.4	0
	Dizziness[b]	19.1	0.3	0
Cardiac disorders	*Electrocardiogram QT prolonged*[b]	21.1	4.8	0
Vascular disorders	*Hypertension*[b]	41.0	19.6	0.1
Gastrointestinal disorders	*Abdominal pain*[b]	33.7	2.5	0
	Diarrhoea[b]	47.0	5.0	0
	Nausea	31.2	1.1	0
	Vomiting	22.4	1.8	0
	Constipation	32.8	0.8	0
	Dry Mouth[b]	43.2	0	0
Skin and subcutaneous tissue disorders	*Rash*[b]	32.8	0.6	0
General disorders and administration site conditions	Pyrexia	17.0	0.1	0
	Fatigue[b]	45.9	3.1	0
	Oedema[b]	48.5	0.8	0
Investigations	*AST increased*[b]	36.7	7.9	0.9
	ALT increased[b]	35.7	10.7	0.8
	Thrombocytopenia[b]	15.5	2.0	1.0
	Lymphopenia	13.9	4.4	0.8
	Hypomagnesaemia	12.6	0.3	0
	Creatinine increased[b,c]	28.5	1.4	0.5
Blood and lymphatic system	*Haemorrhage*[d]	22.0	2.1	0.5

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = number of patients.

[a] Investigators were instructed to report hypersensitivity reactions, characterised 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 through 21).

[b] Composite terms are *italicized*.

[c] Toxicity grade assignment based on CTCAE (v5.0).

[d] See description of selected adverse reactions for further characterisation.

Toxicity grade assignment based on CTCAE (v4.03).

Table 37. Laboratory Adverse Drug Reactions in LIBRETTO-001- Overall Safety Population

System Organ Class	Event	Selpercatinib (N=796)			
		N[a]	Any Grades Toxicity (%)	Grade 3 Toxicity (%)	Grade 4 Toxicity (%)
Investigations[a]	AST increased	791	58.9	9.7	0.9
	ALT increased	791	55.5	10.7	1.0
	Platelets decreased	791	37.4	1.9	1.3
	Lymphocyte count decrease	765	51.8	17.6	1.8
	Magnesium decreased	787	32.9	0.4	0.3
	Creatinine increased[b]	791	47.3	1.5	0.9

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = number of patients.

[a] Based on laboratory assessments. Percentage is calculated based on the number of patients with baseline assessment in the corresponding safety analysis set (N) and at least one postbaseline assessment as the denominator (N'), which was 765 for Lymphocyte count decrease, 787 for Magnesium decreased and 791 for the other PTs.

[b] Toxicity grade assignment based on CTCAE (v5.0)

Toxicity grade assignment based on CTCAE (v4.03).

Table 38. Summary of Treatment-Emergent Adverse Events-Overall Safety Population and NSCLC Safety Population

Term	Treatment-Naïve Patients (N=69)	Patients Previously Treated with Platinum-Based Chemotherapy (N=248)	NSCLC Safety Population (N=356)	Overall Safety Population (N=796)
Any TEAEs, n (%)	69 (100.0)	248 (100.0)	356 (100.0)	795 (99.9)
Related to selpercatinib	67 (97.1)	235 (94.8)	341 (95.8)	756 (95.0)
Grade ≥3 TEAEs, n (%)	50 (72.5)	182 (73.4)	263 (73.9)	572 (71.9)
Related to selpercatinib	25 (36.2)	107 (43.1)	143 (40.2)	307 (38.6)
TEAEs leading to treatment discontinuation, n (%)	7 (10.1)	24 (9.7)	34 (9.6)	64 (8.0)
Related to selpercatinib	3 (4.3)	8 (3.2)	11 (3.1)	25 (3.1)
TESAE, n (%)	26 (37.7)	123 (49.6)	173 (48.6)	353 (44.3)
Related to selpercatinib	8 (11.6)	38 (15.3)	52 (14.6)	87 (10.9)
Fatal TEAEs, n (%)	4 (5.8)	14 (5.6)	24 (6.7)	45 (5.7)
Related to selpercatinib	0	0	0	1 (0.1)

Percentage is calculated based on 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 selpercatinib.
Related events are those judged by the Investigator as related to selpercatinib.
Severity grade assignment based on CTCAE (v4.03): Grade 3 (severe), Grade 4 (life-threatening/debilitating), Grade 5 (fatal).

The most frequent TEAEs occurring in 30% or more in the Overall Safety Population were *edema*, *diarrhea*, *fatigue*, *dry mouth*, *hypertension*, *aspartate aminotransferase* (*AST) increased*, *alanine aminotransferase* (*ALT) increased*, *constipation*, *rash*, *abdominal pain*, and *nausea.*

The most frequent TEAEs of any grade occurring 30% or more in the NSCLC Safety Population were *edema*, *diarrhea*, *fatigue*, *dry mouth*, *hypertension*, *AST increased*, *ALT increased*, *nausea,* and *rash.*

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

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

Serious adverse event/deaths/other significant events

Serious AEs

Table 39. Serious Treatment-emergent Adverse Events and Related to Study Drug

Preferred Term	Integrated (N=248) n (%)	SAS1 (N= 69) n (%)	RET Fusion-positive NSCLC (N=356) n (%)
Patients with TESAEs Related to Study Drug	38 (15.3)	8 (11.6)	52 (14.6)
Drug hypersensitivity	8 (3.2)	1 (1.4)	10 (2.8)
Alanine aminotransferase increased	4 (1.6)	1 (1.4)	6 (1.7)
Aspartate aminotransferase increased	4 (1.6)	1 (1.4)	6 (1.7)
Hypersensitivity	1 (0.4)	1 (1.4)	4 (1.1)
Hypertension	3 (1.2)	0 (0.0)	3 (0.8)
Pleural effusion	2 (0.8)	1 (1.4)	4 (1.1)
Ascites	3 (1.2)	0 (0.0)	3 (0.8)
Dehydration	0 (0.0)	0 (0.0)	2 (0.6)
Diarrhoea	1 (0.4)	0 (0.0)	2 (0.6)
Pericardial effusion	2 (0.8)	0 (0.0)	2 (0.6)
Chylothorax	2 (0.8)	0 (0.0)	2 (0.6)
Constipation	1 (0.4)	1 (1.4)	2 (0.6)
Drug-induced liver injury	1 (0.4)	0 (0.0)	1 (0.3)
Fatigue	1 (0.4)	0 (0.0)	1 (0.3)
Haemorrhage intracranial	1 (0.4)	0 (0.0)	1 (0.3)
Nausea	0 (0.0)	1 (1.4)	1 (0.3)
Thrombocytopenia	1 (0.4)	0 (0.0)	1 (0.3)
Cardiac failure	1 (0.4)	0 (0.0)	1 (0.3)
Colitis	1 (0.4)	0 (0.0)	1 (0.3)
Drug eruption	1 (0.4)	0 (0.0)	1 (0.3)
Dysphagia	1 (0.4)	0 (0.0)	1 (0.3)
Electrocardiogram T wave inversion	0 (0.0)	1 (1.4)	1 (0.3)
Focal segmental glomerulosclerosis	1 (0.4)	0 (0.0)	1 (0.3)
Hypothyroidism	1 (0.4)	0 (0.0)	1 (0.3)
Ischaemic stroke	1 (0.4)	0 (0.0)	1 (0.3)
Liver function test increased	1 (0.4)	0 (0.0)	1 (0.3)
Mental disorder	1 (0.4)	0 (0.0)	1 (0.3)
Retroperitoneal haematoma	0 (0.0)	1 (1.4)	1 (0.3)

Percentage is calculated based on 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-292.
Patients are counted once within each preferred term.
Reported adverse event terms were coded using MedDRA (version 21.0).
Adverse events are sorted in descending frequency based on the overall count in the overall safety analysis set.

Deaths

Table 40. List of Patients with Grade 5 Adverse Events (NSCLC Safety Population)

	Integrated (N=248) n (%)	SAS1 (N= 69) n (%)	RET Fusion-positive NSCLC (N=356) n (%)
Within 28 Days of Last Dose	19 (7.7)	5 (7.2)	33 (9.3)
Disease Progression	11 (4.4)	2 (2.9)	15 (4.2)
Adverse Event	8 (3.2)	3 (4.3)	17 (4.8)
Other	0 (0.0)	0 (0.0)	1 (0.3)
More than 28 Days after Last Dose	59 (23.8)	15 (21.7)	78 (21.9)
Disease Progression	43 (17.3)	12 (17.4)	58 (16.3)
Adverse Event	5 (2.0)	1 (1.4)	6 (1.7)
Other	11 (4.4)	2 (2.9)	14 (3.9)

One patienthad a grade 5 treatment-emergent adverse event with fatal outcome in the adverse event form, but primary death reason was disease progression

Table 41. Death events occurring within 28 days from the last dose of selpercatinib (NSCLC Safety Population)

Preferred Term	Integrated (N=248) n (%)	SAS1 (N= 69) n (%)	RET Fusion-positive NSCLC (N=356) n (%)
Patients with TEAEs with Outcome Fatal	14 (5.6)	4 (5.8)	24 (6.7)
Respiratory failure	3 (1.2)	1 (1.4)	6 (1.7)
Sepsis	2 (0.8)	0 (0.0)	2 (0.6)
Cardiac arrest	2 (0.8)	0 (0.0)	4 (1.1)
Acute respiratory failure	1 (0.4)	0 (0.0)	1 (0.3)
Pneumonia	1 (0.4)	0 (0.0)	2 (0.6)
Cardio-respiratory arrest	0 (0.0)	1 (1.4)	1 (0.3)
Cerebral haemorrhage	2 (0.8)	0 (0.0)	2 (0.6)
Dyspnoea	0 (0.0)	1 (1.4)	1 (0.3)
Corona virus infection	1 (0.4)	0 (0.0)	1 (0.3)
Hypoxia	1 (0.4)	0 (0.0)	1 (0.3)
Multiple organ dysfunction syndrome	1 (0.4)	0 (0.0)	1 (0.3)
Somnolence	0 (0.0)	1 (1.4)	1 (0.3)
Sudden death	0 (0.0)	0 (0.0)	1 (0.3)

Adverse Events of Special Interest

Table 42. Adverse Events of Special Interests Reported in LIBRETTO-001 as of the 15 June 2021 Data Cut-Off Overall Safety Population and Treatment-Naïve Patients

AESI	Overall Safety Population (N=796)	Treatment-Naïve Patients (N=69)
Liver injury AST/ALT increased[a]	• TEAEs of AST increased in 36.7% and ALT increased in 35.7%; reported as related to selpercatinib: AST increased 28.8% and ALT increased 28.5% • Most were Grade 1 or 2 • Grade 3 AST increased in 7.9% and ALT increased 10.7% • Grade 4 AST increased in 0.9% and ALT increased in 0.8% • No Grade 5 events • TESAEs: AST increased in 1.5% and ALT increased in 1.5%; reported as related to selpercatinib: AST increased in 1.1% and ALT increased in 1.1% • Median time to first onset of AST and ALT increased was 6.0 and 5.8 weeks • Dose withheld in 10.7% (AST increased) and 11.8% (ALT increased). Dose reduction in 7.2% (AST increased) and 7.8% (ALT increased) • Permanent discontinuations in only 0.5% (AST increased) and 0.6% (ALT increased)	• TEAEs of AST increased in 46.4% and ALT increased 42.0%; reported as related to selpercatinib: AST increased in 37.7% and ALT increased in 34.8% • Most were of Grade 1 or 2 • Grade 3 AST increased in 7.2% and ALT increased: in 14.5% • No Grade 4 or 5 events • TESAEs: AST increased in 1.4% and ALT increased in 1.4%; reported as related to selpercatinib: AST increased in 1.4% and ALT increased in 1.4% • Median time to first onset of both AST and ALT increased was 4.1 weeks • Dose withheld in 15.9% (AST increased) and 17.4% (ALT increased). Dose reduction in 10.1% (AST increased) and 14.5% (ALT increased) • Permanent discontinuation in 1.4%
Liver injury Drug related hepatic disorders based on SMQs[b]	• 58.0% of patients reported a TEAE from this SMQ; reported as related to selpercatinib in 43.0% • TEAEs in ≥10% of patients were AST increased, ALT increased, blood ALP increased, ascites, hypoalbuminaemia, and blood bilirubin increased • Most were Grade 1 and 2 • Grade 3 or 4 TEAEs: 15.7% and 2.0%, respectively • No Grade 5 events • TESAEs: 3%; reported as related to selpercatinib in 2.3% • Median time to first onset was 4.3 weeks • Dose withheld in 18.2% and dose reduction in 13.2% • Permanent discontinuation in 1% **Hepatocellular Injury based on Hy's Law** An analysis to identify potential cases of liver injury with impairment of liver function using the criteria for Hy's law was performed. • 4 NSCLC patients (none were treatment-naïve patients), potentially met the laboratory criteria for Hy's Law (ALT or AST ≥ 3 × ULN,	• 58.0% of patients reported a TEAE from this SMQ; reported as related to selpercatinib in 43.5% • TEAEs in ≥10% of patients were AST increased, ALT increased, blood bilirubin increased, hypoalbuminaemia, and blood ALP increased • Most were Grade 1 or 2 • Grade 3: 20.3% • No Grade 4 or Grade 5 events • TESAEs: 1.4%; all reported as related to selpercatinib • Median time to first onset was 4.1 weeks • Dose withheld in 24.6% and dose reduction in 17.4% • Permanent discontinuations in 1.4%

	and a concurrent increase in TBL > 2 × ULN and ALP < 2 × ULN) • In all 4 cases other factors were present that may have led to the elevated laboratory findings (history of liver metastasis and/or diagnosis of new liver lesions around the time of the event 3 patients; initiation of nitrofurantoin (a known hepatoxic agent) 1 patient). Therefore, none of the cases met the criteria for Hy's law.	
Hypertension[c]	• Any-grade *hypertension* in 41.0%; reported as related to selpercatinib in 28.1% • Grade 3: 19.6%; Grade 4: 0.1% • No Grade 5 events • TESAEs: 0.9%; reported as related to selpercatinib in 0.6% • Median time to first onset: 4.1 weeks • Dose withheld in 6.3% and dose reduction in 1.3% • Permanent discontinuation due to hypertension in 0.1% In addition to the analysis using the composite term for hypertension an analysis using the MedDRA SMQ (narrow scope) for hypertension was conducted. Based on this review the incidence of events of any grade was 41.1%. The increase was due to reports of the TEAEs essential hypertension and secondary hypertension. No significant new information was identified from the additional analysis.	• Any-grade *hypertension* in 44.9%; reported as related to selpercatinib in 26.1% • Grade 3: 20.3% • No Grade 4 or Grade 5 events • No TESAEs • Median time to first onset: 6.3 weeks • Dose withheld in 7.2% and dose reduction in 1.4% • No permanent discontinuation due to hypertension No additional TEAEs were identified in the Treatment-Naïve Patients.
Hypersensitivity[d]	• Any-grade *hypersensitivity* in 5.9%; reported as related to selpercatinib in 4.4% • Most were Grade 1 or 2 • Grade 3: 1.9% • No Grade 4 or Grade 5 events. • The median time to first onset: 1.9 weeks • TESAEs: 2.0%; all related to selpercatinib • Dose withheld in 4.0% and dose reduction in 3.9% • Permanent discontinuation due to hypersensitivity in 0.4% In addition to the analysis using the composite term for hypersensitivity an analysis using a broader list of MedDRA PTs[d] potentially associated with hypersensitivity was conducted. Based on this review the incidence of any grade events was 6.5%. The increase was due to reports of the TEAEs drug eruption. No additional reports were identified in the Treatment-Naïve Patients. No significant new information was identified from the additional analysis.	• Any-grade *hypersensitivity* in 7.2%; reported as related to selpercatinib in 5.8%**Error! Reference source not found.** • Most events were Grade 1 or 2 • Grade 3: 4.3% • No Grade 4 or Grade 5 events • The median time to first onset: 1.4 weeks • TESAEs 2.9% patients; all related to selpercatinib • Dose withheld in 4.3% and dose reduction in 4.3% • Permanent discontinuation due to hypersensitivity in 1.4%
Electrocardiogram QT Interval	• Any-grade *electrocardiogram QT prolonged* in 21.1%; reported as related to selpercatinib in 16.3%	• *Electrocardiogram QT prolonged* in 20.3%; reported as related to selpercatinib in 14.5%
Prolongation[e]	• Most events were Grade 1 or Grade 2 • Grade 3: 4.8% • No Grade 4 or Grade 5 events • TESAEs: 0.1%; none reported as related to selpercatinib • Dose withheld in 4.4% and dose reduction in 3.1% • No permanent discontinuation due to *ECG QT prolongation* No clinically significant TEAE related to QT prolongation such as treatment-emergent ventricular tachycardia, ventricular fibrillation, or Torsades de Pointes have been observed in the clinical development program. There was 1 report of sudden death (assessed as unrelated to selpercatinib) in a patient with significant cardiac history who experienced episodes of prolonged QT during the course of the study	• Most events were Grade 1 or Grade 2 • Grade 3: 5.8% • No Grade 4 or Grade 5 events • No TESAEs • Dose withheld in 4.3% and dose reduction in 1.4%. • No permanent discontinuation due to *ECG QT prolongation.*

Abbreviations: ALP = aspartate aminotransferase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = Standardised MedDRA Query.

[a] Analysis of 'AST/ALT increased' was based on composite AE terms (PTs of 'AST increased' are 'Aspartate aminotransferase increased' and 'Aspartate aminotransferase abnormal'; PT terms for 'ALT increased' are 'Alanine aminotransferase increased' and 'Alanine aminotransferase abnormal').

[b] Analysis of events related to liver injury was performed based on drug-related hepatic disorders – comprehensive search [SMQ]. Interim CSR Table 8.150 provides the PT terms for "liver injury".

[c] Analysis of events related to hypertension was performed based on SMQ of hypertension (narrow scope PTs). PTs for composite term *hypertension* were hypertension, blood pressure increased, and blood pressure abnormal.

[d] PTs for composite term *hypersensitivity* were hypersensitivity and drug hypersensitivity. PTs used in the additional hypersensitivity analysis were hypersensitivity, drug hypersensitivity, Type IV hypersensitivity reaction, Type III immune complex mediated reaction, Type II hypersensitivity, toxic epidermal necrolysis, Stevens-Johnson syndrome, SJS-TEN overlap, serum sickness-like reaction, serum sickness, drug reaction with eosinophilia and systemic symptoms, drug eruption, acute generalised exanthematous pustulosis.

[e] PTs for composite term *Electrocardiogram QT prolonged* were ECG QT prolonged and ECG QT interval abnormal.

►AST and ALT increases were reported in 36.7% and 37.6% of patients in the Overall Safety Population and 41.9% and 41.3% of patients in the NSCLC Safety Population, respectively. Majority were of Grade 1 or 2.

►The incidence of any-grade hypertension was 41% and 20% were Grade ≥3 in the Overall Safety Population. Patients with a documented history of hypertension displayed a higher incidence of treatment-emergent Grade 3 hypertension than patients without (28% versus 14%, respectively).

►Electrocardiogram QT prolonged was reported as a TEAE in similar proportion of the patients in both the Overall (20.8%) and NSCLC (21.1%) Safety Populations. Most patients had TEAEs of Grade 1 or 2 in severity in both the Overall Safety (16.3%) and NSCLC safety (14.9%) population.

►The overall incidence of any-grade hypersensitivity was 5.9% in the Overall Safety Population. A total of 15 patients (1.9%) in the Overall Safety and 12 patients (3.4%) in the NSCLC Safety Population had Grade 3 hypersensitivity.

Other Adverse Events

Table 43. Other Adverse Events Reported in LIBRETTO-001 as of the 15 June 2021 Data Cut

Other adverse events reported in LIBRETTO-001 based on the Overall Safety Population (N=796)	
Hyponatraemia (Selected terms from hyponatraemia SMQ)[a]	• Any-grade hyponatraemia in 14.1%; related to selpercatinib in 3.1% • Grade 3 or 4 events: 8.0% • No Grade 5 events • TESAEs: 2.3%; none related to selpercatinib • Dose withheld in 2.3% and dose reduction in 0.4% • No permanent discontinuation due to hyponatraemia
Acute Kidney Injury (Acute Kidney Injury SMQ)	• Any-grade acute kidney injury (SMQ) in 32.8%; related to selpercatinib in 18.2%. Of note this includes events of creatinine increased, which is a recognised ADR for selpercatinib • Grade 3 or 4 events: 2.6% • No Grade 5 events • TESAEs: 1.3%; none related to selpercatinib • The most frequently reported events (≥5%) were: o Blood creatinine increased (any-grade 25.6%; Grade ≥3 0.8%) o Proteinuria (any-grade 6.7%; Grade ≥3 0.6% o Acute kidney injury (any-grade 5.2%; Grade ≥3 1.5%) • Dose withheld in 4.5% and dose reduction in 2.6% • Permanent discontinuation due to acute kidney injury: 0.1%
Dysphagia (MedDRA PTs: dysphagia, malignant dysphagia and radiation dysphagia)	• Any-grade dysphagia in 7.3%; related to selpercatinib in 1.0% • Grade 3 events: 0.9% • No Grade 4 or 5 events • TESAEs: 1.1%; related to selpercatinib in 0.1% • Dose withheld in 1.0% and dose reduction in 0.1% • Permanent discontinuation due to dysphagia: 0.3%
Pulmonary Disorders (Respiratory, Thoracic and Mediastinal Disorders SOC)	• Any-grade pulmonary disorders in 60.2%; related to selpercatinib in 18.3% • Grade 3 or Grade 4 events: 8.9% • Grade 5 events 2.0% • TESAEs: 9.2%; related to selpercatinib in 1.0% • The most frequently reported events (≥10%) were: o Dyspnoea (any-grade 18.8%; Grade ≥3 3.1%) o Cough (any-grade 19.2%; Grade ≥3 0.0%) o Pleural effusion (any-grade 12.1%; Grade ≥3 2.6%)

Other adverse events reported in LIBRETTO-001 based on the Overall Safety Population (N=796)	
	○ Dysphonia (any-grade 10.7%; Grade ≥3 0.1%) • Dose withheld in 7.5% and dose reduction in 2.8% • Permanent discontinuation due to pulmonary disorders: 1.1%
Sepsis (Sepsis SMQ)	• Any-grade Sepsis (SMQ) in 3.0%; related to selpercatinib in 0.1% • Grade 3 or 4 events: 2.1% • Grade 5 events: 0.9% • TESAEs: 2.5%; None related to selpercatinib • Dose withheld in 1.6% and no dose reductions • Permanent discontinuation due to sepsis: 0.8%
Haemorrhages (haemorrhage laboratory terms [narrow scope] SMQ, and haemorrhage terms [excluding laboratory terms] SMQ)[b]	• Any-grade haemorrhages in 22.0%; related to selpercatinib in 4.1% • Grade 3 or 4 events: 2.6% • Grade 5 events: 0.5% • TESAEs: 2.8%; related to selpercatinib in 0.4% • The most frequently reported events (≥2%) were: ○ Epistaxis (any-grade 6.0%; Grade ≥3 0%) ○ Haematuria (any-grade 3.6%; Grade ≥3 0%) ○ Haemoptysis (any-grade 2.4%; Grade ≥3 0.3%) ○ Contusion (any-grade 2.4%; Grade ≥3 0.1%) • Dose withheld in 3.0% and dose reductions in 0.3% • Permanent discontinuation due to sepsis: 0.4%

Abbreviations: ADR = adverse drug reaction; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

[a] Blood sodium abnormal, blood sodium decreased, hyponatraemia, hyponatraemic coma, hyponatraemic encephalopathy, hyponatraemic syndrome, hypoosmolar state.

Laboratory findings

The highest incidence of any grade treatment-emergent abnormality across hematology parameters was reported for decreased lymphocyte count (51.8% and 56.3%) and decreased white blood cell count (48.7% and 55.1%) in both the Overall Safety Population and the NSCLC Safety Population, respectively.

The highest incidence of treatment-emergent serum abnormality was reported for AST increased (58.9% and 66.2%) and ALT increased (55.5% and 63.9%) in both the Overall Safety Population and the NSCLC Safety Population, respectively. The most commonly reported abnormalities (increase or decrease) across serum chemistry parameters were primarily Grade 1.

Safety in special populations

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

Safety related to drug-drug interactions and other interactions

Please refer to the Pharmacokinetics section.

Discontinuation due to adverse events

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

The most frequently reported TEAEs leading to a dose reduction in 5% or more patients in both the Overall Safety Population and Treatment-Naïve Patients were ALT increase and AST increase the increase and AST increase

The most frequently reported TEAEs leading to permanent discontinuation of selpercatinib in 4 or more patients in the Overall Safety Population were ALT increased, fatigue, AST increase, and sepsis. All other AEs occurred in less than 4 patients. In Treatment-Naïve Patients no events leading to permanent discontinuation of selpercatinib were reported in more than 1 patient.

Post marketing experience

As of April 2021, Selpercatinib was approved in 34 countries including those in the EU, the US and Switzerland for treatment of patients with RET fusion-positive NSCLC, RET fusion-positive thyroid cancer and RET-mutant medullary thyroid cancer. Specific patient populations and dosing guidance vary by country. Cumulatively, up to the 30 April 2021, an estimated 590 patients were exposed to selpercatinib worldwide. The data reported from the post marketing setting, is generally consistent with the known safety profile of selpercatinib. Most events were reported as non-serious and the most frequently reported events were recognised ADRs for selpercatinib or clinically expected in the target indication. Overall, no new significant safety information has been identified from post marketing sources. The periodic safety update report/periodic benefit-risk evaluation report with a data lock of 08 May 2021 confirmed and supported the previously established favourable benefit-risk profile for selpercatinib in the currently approved indications.

2.5.1. Discussion on clinical safety

Safety was evaluated in patients in the Overall Safety Population (N=796) and in the NSCLC Safety Population (N=356) who received at least 1 dose of selpercatinib as of the data cutoff date of 15 June 2021.

In terms of exposure, the median time on treatment was 21.29 and 19.09 months, respectively, for the Overall Safety Population and NSCLC Safety Population. In the Treatment-Naïve Population (n=69), the median treatment duration is 18.5 months (range: 0.4 to 41.2 months) and 70% of patients were on treatment for at least 12 months.

The median relative dose intensity was similar for the Overall Safety Population (94.1%) and the NSCLC Safety Population (92.7%).

The most reported dose modification was dose withheld (72.9% in the Overall Safety Population and 77.5% in the NSCLC Safety Population) primarily attributed to adverse events (AEs) (64.1% in the Overall Safety Population and 68.8% in the NSCLC Safety Population).

The types and incidence rates of AEs leading to doses being withheld, dose reductions, and treatment discontinuation were consistent between the Overall Safety Population and Treatment-Naïve Patients.

The most frequent TEAEs occurring in 30% or more patients in both the Overall Safety Population and Treatment-Naïve Patients were oedema, diarrhoea, fatigue, dry mouth, hypertension, AST increased, ALT increased, constipation, rash, abdominal pain, and nausea.

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

The most frequent TESAEs reported in 2% or more patients both in the Overall Safety Population and Treatment-Naïve Patients were pleural effusion, dyspnoea, and hyponatraemia.

Fatal TEAEs were reported in 21 patients at the initial MAA compared with 45 patients at the 15 June 2021 data cut-off. In Treatment-Naïve Patients, a fatal (Grade 5) TEAE was experienced by a total of 4 patients (6%), including 1 patient who died more than 28 days after the last dose of selpercatinib. None in the NSCLC Safety Population were reported by the investigator as treatment-related.

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

The safety profile observed in the data from the 15 June 2021 cut-off remains consistent with previously reported data. No new ADRs or AESIs have been identified since initial authorisation and the safety profile is consistent between the Treatment-Naïve Patients and the Overall Safety Population.

2.5.2. Conclusions on clinical safety

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

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 1.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

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

No changes to the list of safety concerns were made as a result of the data submitted for this new indication.

Pharmacovigilance plan

There are no additional pharmacovigilance activities in place for this product. Routine pharmacovigilance remains sufficient to investigate the risks of selpercatinib.

Risk minimisation measures

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
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

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Growth plate abnormalities in paediatric patients	**Routine risk minimisation measures:** SmPC Section 4.2 and 5.3 **Additional risk minimisation measures:** Not Applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Exposure and safety in patients with severe hepatic impairment	**Routine risk minimisation measures:** A clinical pharmacology study assessing the effect of hepatic impairment on the pharmacokinetics of selpercatinib is completed. SmPC is updated based on the safety and pharmacokinetics data. **Additional risk minimisation measures:** Not Applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study: None
Exposure and safety in patients with cardiac impairment	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** Not Applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study: None

Routine minimisation measures remain sufficient to mitiagate the risks of selpercatinib.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.5, 4.8 and 5.1 of the SmPC have been updated.

2.7.1. User consultation

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

The proposed revisions do not significantly affect the overall readability. It is not considered necessary to conduct consultation with target patient groups further to that performed for the initial MAA.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH is seeking an extension of indication of selpercatinib (RETSEVMO) currently authorised in patients with RET fusion-positive NSCLC previously treated with platinum-based chemotherapy to include the first-line setting.

The agreed indication is: as monotherapy for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.

3.1.2. Available therapies and unmet medical need

Although patients with RET fusion-positive NSCLC have an identifiable driver alteration, until recently, they received the same standard-of-care treatment as patients with NSCLC who do not have a driver alteration, as there were no RET-targeted approved therapies. Standard first-line systemic treatment is platinum doublet-based cytotoxic chemotherapy and/or a checkpoint inhibitor. Available options include pembrolizumab, atezolizumab, bevacizumab, and pemetrexed, all in combination with platinum-based chemotherapy regimens. Pembrolizumab monotherapy is only an option for patients with significant PD-L1 expression.

In the second line setting, the preferred treatment strategy is systemic immune checkpoints inhibitors, as nivolumab, pembrolizumab or atezolizumab, or other systemic therapy as docetaxel, pemetrexed or ramucirumab with docetaxel, nintedanib with docetaxel, among others.

As of November 2021, pralsetinib (GAVRETO) a selective RET inhibitor, has received conditional approval in patients with advanced RET fusion-positive NSCLC.

3.1.3. Main clinical studies

Clinical safety and efficacy of selpercatinib in treatment-naive patients with RET fusion-positive NSCLC are based on analyses of interim data from LIBRETTO-001 (LOXO-RET-17001).

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

3.2. Favourable effects

Treatment-naïve

At data cut-off 15 June 2021, 69 treatment-naïve patients were efficacy evaluable and the ORR (IRC assessment) was 84.1% (95% CI: 73.3, 91.8). Four (4) patients exhibited a confirmed CR and 54 patients experienced PR. ORR according to investigator assessment was in line with the IRC assessment (ORR 85.5% [95% CI: 75; 92.8]).

The median TTR was 1.81 months and, in 66% of responders, DOR was more than 12 months. Median DoR was 20.21 (13.0-NE), with a median duration of follow-up of 20.27 months. However, a stable median cannot yet be estimated.

The median PFS (IRC) was 22.0 months (95% CI: 13.8, NE+), with 29/69 (42%) events observed and median follow-up of 21.9 months. Median OS was not reached at the time of the DCO (29% of events observed). The OS rate was 92.7% at 12 months, 69.3% at 24 months, and 57.1% at 36 months. Efficacy of selpercatinib seems consistent across most important subgroups.

3.3. Uncertainties and limitations about favourable effects

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

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

These limitations will be addressed post authorisation with the submission of updated data and longer follow-up from the LIBRETTO-001 study and the conduct of LIBRETTO-431, a randomised phase III trial in patients with locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC.

3.4. Unfavourable effects

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

Safety was evaluated in patients in the Overall Safety Population (N=796) and in the NSCLC Safety Population (N=356) who received at least 1 dose of selpercatinib as of the data cutoff date of 15 June 2021.

In terms of exposure, the median time on treatment was 21.29 and 19.09 months, respectively, for the Overall Safety Population and NSCLC Safety Population. In the Treatment-Naïve Population (n=69), the median treatment duration is 18.5 months (range: 0.4 to 41.2 months) and 70% of patients were on treatment for at least 12 months.

The median relative dose intensity was similar for the Overall Safety Population (94.1%) and the NSCLC Safety Population (92.7%).

The most reported dose modification was dose withheld (72.9% in the Overall Safety Population and 77.5% in the NSCLC Safety Population) primarily attributed to adverse events (AEs) (64.1% in the Overall Safety Population and 68.8% in the NSCLC Safety Population).

The types and incidence rates of AEs leading to doses being withheld, dose reductions, and treatment discontinuation were consistent between the Overall Safety Population and Treatment-Naïve Patients.

The most frequent TEAEs occurring in 30% or more patients in both the Overall Safety Population and Treatment-Naïve Patients were oedema, diarrhoea, fatigue, dry mouth, hypertension, AST increased, ALT increased, constipation, rash, abdominal pain, and nausea.

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

The most frequent TESAEs reported in 2% or more patients both in the Overall Safety Population and Treatment-Naïve Patients were pleural effusion, dyspnoea, and hyponatraemia.

Fatal TEAEs were reported in 21 patients at the initial MAA compared with 45 patients at the 15 June 2021 data cut-off. In Treatment-Naïve Patients, a fatal (Grade 5) TEAE was experienced by a total of 4 patients (6%), including 1 patient who died more than 28 days after the last dose of selpercatinib. None in the NSCLC Safety Population were reported by the investigator as treatment-related.

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. Data on long-term safety is also lacking. Long-term follow-up from the LIBRETTO-001 and the randomised phase 3 study LIBRETTO-431, to be submitted post approval, will address these uncertainties.

3.6. Effects Table

Table 44. Effects Table for Retsevmo in advanced RET-fusion positive NSCLC (data cut-off: 15 June 2021).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Treatment-Naïve Patients (n=69)						
ORR	rate	% (95% CI)	58 (84.1) (73.3, 91.8)	NA	uncontrolled data	
DOR	median	Months (95% CI)	20.21 (13.0, NE)	NA	Immature and uncontrolled data	
PFS	median	Months (95% CI)	21.95 (13.8, NE)	NA	Immature and uncontrolled data	
OS	median	Months (95% CI)	92.7 at 12 months (83.3, 96.9) 69.3 at 24 months (55.2, 79.7) 57.1 at 36 months (35.9, 73.6)	NA	Immature and uncontrolled data	
Unfavourable Effects						
Treatment-Naïve Patients (n=69)						
Any TEAEs Related to selpercatinib	rate	n (%)	69 (100.0) 67 (97.1)	NA	uncontrolled data	
Grade ≥3 TEAEs Related to selpercatinib	rate	n (%)	50 (72.5) 25 (36.2)	NA	uncontrolled data	
TEAEs leading to treatment discontinuation Related to selpercatinib	rate	n (%)	7 (10.1) 3 (4.3)	NA	uncontrolled data	
TESAE Related to selpercatinib	rate	n (%)	26 (37.7) 8 (11.6)	NA	uncontrolled data	
Fatal TEAEs Related to	rate	n (%)	4 (5.8) 0	NA	uncontrolled data	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
selpercatinib						

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

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Data supporting this application are based on one single-arm trial (LIBRETTO-001), which make interpretation of time to event endpoints and any potential long-term benefit challenging. Nevertheless, this approach is acceptable in the context of a CMA for a product intended for a rare population with an unmet medical need as long as the effect observed in ORR is outstanding and durable.

For treatment naïve patients, clinical data from a larger and more mature dataset of patients are available (median follow-up time of 20 months). The obtained ORR of 84% is considered clinically meaningful. Available results suggest that these responses are durable (mDOR 20 months) and K-M estimates for median PFS and OS allow to anticipate lasting benefits from treatment. Of note, the ORR benefit for the intended population was observed with selpercatinib regardless of line of treatment, with higher ORR in the treatment-naïve population.

Although, other approved front-line therapies with established benefit exist (platinum based doublets/immune checkpoint inhibitor), efficacy with selpercatinib is considered compelling and of sufficient magnitude. Indirect comparisons of available results (KM estimates of PFS and OS) with selpercatinib against those reported with chemo-immunotherapy in 'all-comer' NSCLC patients in studies IMpower130, IMpower150 and KEYNOTE-189 seem promising and give some support to the benefit of targeted treatment in the first line. In addition, clinically meaningful intracranial responses are observed with selpercatinib in patients with CNS metastases, which represents a significant advantage over standard chemotherapy approaches.

In November 2021, another RET inhibitor Gavreto (pralsetinib) was granted a conditional approval in the target population which outlines the advantage of targeted RET treatment: the single-arm ARROW trial showed an ORR of 64% and mDOR of 22.3 months in 233 patients with advanced RET fusion-positive NSCLC. ORR among treatment naïve patients was 72.0% (60.4%, 81.8%).

The safety profile observed in the updated data from the 15 June 2021 cut-off remains consistent with previously reported data. No new ADRs or AESIs have been identified since initial authorisation and the safety profile is consistent between the Treatment-Naïve Patients and the Overall Safety Population.

3.7.2. Balance of benefits and risks

The provided results from LIBRETTO-001 have shown efficacy in term of confirmed response for the treatment of this rare subtype of NSCLC. Responses seem durable and independent of treatment line. However, given the remaining uncertainties mostly related to the uncontrolled design of the pivotal study with the low number of treatment-naïve subjects (n=69), comparative data from the phase 3 study (J2G-MC-JZJC, LIBRETTO-431) together with further follow-up data from the pivotal trial LIBRETTO-001 are required as confirmatory evidence (SOBs).

3.7.3. Additional considerations on the benefit-risk balance

As comprehensive data on the product are also not available in the first-line treatment of RET fusion-positive NSCLC, a conditional marketing authorisation was requested by the applicant for this extension of indication. 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 life-threatening disease.

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

- The benefit-risk balance is positive, as discussed above.
- It is likely that the applicant will be able to provide comprehensive data. The applicant will provide confirmatory data from the ongoing LIBRETTO-431 study, an open-label randomised phase 3 study comparing selpercatinib to a standard-of-care regimen with platinum-based pemetrexed therapy with or without pembrolizumab for treatment-naïve patients with RET fusion-positive nonsquamous NSCLC. This study is currently recruiting and the submission of the final clinical study report (CSR) is expected by 31 December 2024. As of 26 October 2021, the study is approximately 70% enrolled, with approximately 28% of patients coming from EU countries. Enrolment is projected to be completed in the first half of 2022 Results of the LIBRETTO-431 study are intended to provide a comprehensive data package and potentially convert the conditional MA into a full MA.
- Unmet medical need will be addressed, as selpercatinib is considered to provide a major therapeutic advantage over existing therapies based on a differential safety profile, the convenience of oral administration, and the provision of a treatment with a novel mechanism of action of such a magnitude that allows to expect that selpercatinib would be at least similarly active to first line available chemotherapy, immunotherapy or immunochemotherapy options.
- 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 Selpercatinib in advanced RET fusion-positive NSCLC patients regardless of line of therapy is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include the first-line treatment of RET fusion-positive NSCLC for Retsevmo

based on results from study LIBRETTO-001, an open-label, multicentre, global Phase 1/2 study of selpercatinib in patients with RET-altered advanced solid tumours; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. In addition, section 5.1 of the SmPC is revised to reflect updated efficacy data in previously treated RET-fusion positive NSCLC based on a data cut-off of 15 June 2021. The Package Leaflet is updated in accordance. Version 1.3 of the RMP has also been submitted.

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

Amendments to the marketing authorisation

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

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Retsevmo-H-C-005357-II-0011'

Attachments

1. SmPC, Labelling, Package Leaflet (changes highlighted) as adopted by the CHMP on 22 April 2022

Appendix

Not applicable