21 March 2024
EMA/CHMP/143891/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Retsevmo

International non-proprietary name: Selpercatinib

Procedure No. EMEA/H/C/005375/II/0022

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC0-24	area under the concentration versus time curve from time 0 to 24 hours
BID	twice daily
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMA	conditional marketing authorisation
Cmax	maximum drug concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
DOR	duration of response
DCR	disease control rate
EC	European Commission
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ERA	Environmental Risk Assessment
ERB	ethics review board
EUDRA	European Union Drug Regulatory Authorities
GCP	Good Clinical Practices
GMI	growth modulation index
HIPAA	health insurance portability & accountability act
ICF	informed consent form(s)
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug
INV	Investigator assessment
IRB	Institutional Review Board
IRC	Independent Review Committee
MA	marketing authorisation
MedRA	Medical Dictionary for Regulatory Activities
MTC	medullary thyroid cancer
NCA	noncompartmental
NCCN	National Comprehensive Cancer Network
NE	not estimable
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
ORR	objective response rate
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer

ORR	objective response rate
OS	overall survival
PBT	Persistent, bioaccumulative and toxic
PDTC	poorly differentiated thyroid carcinoma
PK	pharmacokinetics
PFS	progression-free survival
PI	principal investigator
PIP	paediatric investigation plan
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	preferred term
PTC	papillary thyroid cancer
QTcF	QT interval corrected for heart rate using Fridericia's formula
RANO	Response Assessment in Neuro-Oncology Criteria
RECIST	Response Evaluation Criteria in Solid Tumors
RET	REarranged during Transfection
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMQ	Standardised MedDRA Queries
TC	thyroid cancer
TEAE	treatment-emergent adverse event (new or worsening AEs with date of onset during or after the date of first study intervention administration through the end of study); this is synonymous with "adverse event" for this report
TE-SAE	treatment-emergent SAE
Tmax	time to maximum plasma concentration
TTR	time to response
TTBR	time to best response
ULN	upper limit or normal
vPvB	very persistent and very bioaccumulative

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 29 November 2022 an application for a variation.

The following variation was requested:

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

Extension of indication for RETSEVMO to include the treatment of adults with advanced or metastatic RET fusion-positive solid tumours with disease progression on or after prior systemic therapies or who have no satisfactory therapeutic options, based on interim data from study LIBRETTO-001 (LOXO-RET-17001); LIBRETTO-001 is an open-label, multicentre, global Phase 1/2 study of selpercatinib in adult and adolescent patients with advanced RET-altered tumours. As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

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 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0369/2019 on the agreement of a paediatric investigation plan (PIP), on the granting of a deferral and on the granting of a waiver for selpercatinib.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Carolina Prieto Fernandez

Timetable	Actual dates
Submission date	29 November 2022
Start of procedure:	31 December 2022
CHMP Rapporteur Assessment Report	24 February 2023
PRAC Rapporteur Assessment Report	2 March 2023
PRAC members comments	8 March 2023
PRAC Outcome	16 March 2023
CHMP members comments	20 March 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 March 2023
Request for supplementary information (RSI)	30 March 2023
CHMP Rapporteur Assessment Report	22 June 2023
PRAC Rapporteur Assessment Report	23 June 2023
PRAC Outcome	6 July 2023
CHMP members comments	10 July 2023
Updated CHMP Rapporteur Assessment Report	13 July 2023
Request for supplementary information (RSI)	20 July 2023
CHMP Rapporteur Assessment Report	11 October 2023
PRAC Rapporteur Assessment Report	12 October 2023
PRAC Outcome	26 October 2023
CHMP members comments	27 October 2023
Updated CHMP Rapporteur Assessment Report	2 November 2023
Request for supplementary information (RSI)	9 November 2023
CHMP Rapporteur Assessment Report	21 December 2023
PRAC Rapporteur Assessment Report	2 January 2024
PRAC Outcome	11 January 2024
CHMP members comments	15 January 2024
Updated CHMP Rapporteur Assessment Report	19 January 2024
Request for supplementary information (RSI)	25 January 2024
CHMP Rapporteur Assessment Report	7 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur Assessment Report	14 March 2024
Opinion	21 March 2024
The CHMP adopted a report on similarity of Retsevmo with Nexavar, Lutathera, Onivyde pegylated liposomal, Zejula, Pemazyre, Kimmtrak, Xermelo, Qarziba, Ayvakyt, Koselugo, Somakit, Qinlock, Crysvita, Cometriq, Tibsovo, Finlee and Spexotras (Appendix 1)	21 March 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The MAH submitted an application for an extension of indication in patients who harbour a *RET* fusion-positive solid tumour, i.e. agnostic indication.

The indication claimed by the applicant is the following:

Retsevmo as monotherapy is indicated for the treatment of adults with advanced or metastatic *RET* fusion-positive solid tumours with disease progression on or after prior systemic therapies or who have no satisfactory therapeutic options.

Epidemiology

Alterations in RET have been implicated in the pathogenesis of several human cancers, including Non-small Cell Lung Cancer (NSCLC), thyroid cancer, and Medullary Thyroid Cancer (MTC), among other tumour types. RET gene-fusions occur most commonly in lung cancer (approximately 1% to 2% of NSCLCs), Papillary Thyroid Cancer (PTC), and poorly differentiated subtypes (PDTC) (approximately 5% to 10% of PTCs and PDTCs), and in extremely rare subsets of other cancers, including breast, colon, oesophageal, ovarian, prostate, stomach, pancreatic, salivary gland cancers, and sarcomas (most occurring at rates of less than 1%) (GENIE cBIO Portal, Kato et al. 2017; Davis et al. 2020; Kohno et al. 2020; Santoro et al. 2020).

Biologic features

Multiple lines of evidence suggest that *RET* fusions are activating genomic events leading to oncogenic addiction regardless of the tumour type in which they arise. *RET* fusions cause transformation *in vitro* and *in vivo* and promote cell proliferation and survival when expressed in human cancer cell lines. They also display the hallmark feature of oncogene addiction and their inhibition in *RET* fusion patient-derived cancer models lead to tumour cell death. These characteristics and effects have been observed for *RET* fusions in both *in vitro* and *in vivo* models for a range of tumour types, including thyroid, lung, colorectal, pancreatic, and breast cancers, as well as mammary adenocarcinoma and melanoma (Takahashi et al. 1985; Portella et al. 1996; Ohshima et al. 2010; Matsubara et al. 2012; Saito et al. 2014; Starenki et al. 2014; Drilon et al. 2018; Gozgit et al. 2018; Paratala et al. 2018; Subbiah et al. 2018). Consistent with this observation, *RET* fusions in tumours identified from patients almost always appear mutually exclusive of other known validated oncogenic drivers, a pattern shared by other bona fide cancer drivers (Farago and Azzoli 2017). The great majority of the epidemiological data available for investigating *RET*-fusion tumours includes all patients identified with a given tumour type, and not only the small subsets with oncogenic drivers, such as *RET*.

RET fusions are not extensively studied in solid tumours aside from lung and thyroid cancers (Li et al. 2019b, Feng et al. 2022). The prevalence of the totality of patients with *RET* fusion-positive tumour is poorly described in literature. Most studies describe the prevalence associated with different indications.

Kato et al. identified *RET* alterations. Among diverse cancer types, *RET* aberrations were identified in 88 cases [1.8% (88/4871)], with mutations being the most common alteration [38.6% (34/88)], followed by fusions [30.7% (27/88), including a novel sequestome1-*RET*] and amplifications [25% (22/88)] (Kato et al. 2017). Ferrara et al. (2017) described an estimated prevalence of *RET* fusion gene between 0.9% to 1.8% in lung adenocarcinoma.

RET fusions provide a viable therapeutic target for oncologic treatment, and further study is warranted into the prevalence and pathogenesis of *RET* fusions as well as development of current and new tyrosine kinase inhibitors (Li et al. 2019a). Per the literature, Kato et al. 2017, *RET* fusion expression was identified in small cohorts of:

- lung carcinosarcoma (16.7%),
- ovarian epithelial carcinoma (1.9%),
- salivary gland adenocarcinoma (3.2%),
- pancreatic ductal adenocarcinoma (0.6%), and
- carcinoma of unknown primary origin (0.7%).

RET aberrations were also identified in 0.2% to 1.6% of all colorectal carcinomas, and *RET* rearrangements were detected in 0.16% of breast cancers (Li et al. 2019b).

Shi et al. (2022) identified that prevalence of functional *RET* fusions was

- 1.05% in lung cancer
- 6.03% in thyroid cancer
- 0.39% in colorectal cancer, and
- less than 0.1% in gastric cancer and hepatocellular carcinoma.

Limited information from European sources is widely available as follows:

- in another large cohort study including Switzerland, the Netherlands and Australia, rearrangement of the RET gene was found in 3 cases of pancreatic cancer (7.5%) (Chou et al. 2020).

Clinical presentation, diagnosis

The natural history, including mortality and morbidity of the totality of patients with *RET* fusion-positive tumour is not well-described in literature. However, based on the limited literature available for *RET* fusion-positive solid tumours, there is no indication that the course of the disease would be meaningfully different to the non-*RET* population.

Management

Patients with advanced or metastatic *RET* fusion-positive solid tumour, for example, colon, pancreatic, salivary gland, or breast cancers and soft tissue sarcoma may have established standards of care in early treatment lines. These may vary widely between tumour types and include surgical resection, radiation therapy, systemic therapy, or combinations of multiple modalities. Systemic therapies can range from oral tyrosine kinase inhibitors or hormone therapy to immunotherapy to multiagent chemotherapy regimens. Differences in standards also exist geographically but recommended or approved regimens are readily available through different treatment guidelines published by relevant medical organisations and

cooperative groups, for example, NCCN, ESMO. Alternately, some patients with *RET* fusion-positive solid tumour, for example, cancer of unknown primary origin, certain skin cancers, and histiocytosis may not have established standards of care due to their rarity.

With the emergence of next-generation sequencing tools, cancer genomic data have become more widely available, and cancer therapy has shifted from a purely histology-based approach towards incorporating a precision medicine-based approach. Novel oncogenic drivers and biomarkers have been described across different tumour types, leading to the development of targeted therapies and the design of innovative trials, many of which are evaluating tissue-agnostic therapies (Weis et al. 2021).

Table 1 shows response rates for available, standard treatment options, as per ESMO guidelines, for tumour types known to harbour RET fusions, which are also applicable to this MAA. Included are tumour types occurring at a 1% or greater frequency in the cBIO database and solid tumours, other than NSCLC and TC, in LIBRETTO-001 that occurred in 2 patients or more.

In most cases, by the time a patient reaches second-line treatment, response rates to available therapy are generally less than 20%, highlighting the unmet medical need for these patients.

There are no available targeted treatment options specifically for patients with these RET fusion-positive cancers, irrespective of line of treatment.

Table 1. Treatment Effect for Representative Standard-of-Care Therapies in Tumour Types That Have Been Shown to Harbour RET Fusions Excluding NSCLC and TC Tumours

Cancer Type	Line of Therapy	Treatment (Cancer Subtype)	N	Response Rate (%) (95% CI[a])	Time to Event Endpoints	Reference
Colorectal	1L	FOLFOX + bevacizumab	53	68% (53.8, 92)	mDOR: 8 mo	Emmanouilides et al. 2007
		CAPEOX + bevacizumab	699[b]	38%	mDOR: 8.5 mo mPFS: 9.4 mo	Saltz et al. 2008
		FOLFIRI + panitumumab	64	82.8%	mPFS: 13 mo (9.6, 16.4)	Geredeli and Yasar 2018
	2L	Irinotecan	132	12% (7.0, 18.1)	NR	Camptosar package insert, 2022
		FOLFIRI + ramucirumab	536	13.4%	mPFS: 5.7 mo (5.5, 6.2)	Tabernero et al. 2015
	3L	FOLFIRI	33	6% (0, 13)	mPFS: 18 wk	Andre et al. 1999
	≥3L	Regorafenib	505	1%	mPFS 1.9 mo	Grothey et al. 2013
		Trifluridine/ Tipiracil	261	1.1%	mPFS: 2 mo (1.9, 2.8)	Xu et al. 2018

Cancer Type	Line of Therapy	Treatment (Cancer Subtype)	N	Response Rate (%) (95% CI[a])	Time to Event Endpoints	Reference
Pancreas	1L	FOLFIRINOX	171	32% (24.7, 39.1)	mDOR: 5.9 mo mPFS: 6.4 mo	Conroy et al. 2011
		Gemcitabine + nab-paclitaxel	431	23% (19, 27)	mDOT: 3.9 mo mPFS: 5.5 mo	Von Hoff et al. 2013
	2L	5-FU + nanoliposomal irinotecan post gemcitabine	117	16%	mPFS: 3.1 mo	Wang-Gillam et al. 2016
		Gemcitabine + nab-paclitaxel post FOLFIRINOX	30	13% (5.3, 29.7)	mPFS: 3.8 mo	Mita et al. 2019
Salivary	1L	Cisplatin + doxorubicin + cyclophosphamide	15	60%	NR	Debaere et al. 2011
		Cisplatin + vinorelbine	40	35% (22.1, 50.4)	mPFS: 6.3 mo	Hong et al. 2017
	2L	No standard				
Unknown primary	1L	Carboplatin + paclitaxel	75	39% (27.5, 49.9)	mDOR: 6 mo	Briasoulis et al. 2000
		Cisplatin + gemcitabine	27	19%	mPFS: 5 mo	Gross-Goupil et al. 2012
	2L	No standard				
Breast	1L, HER2-	Palbocicli+ exemestane OR fulvestrant	206	26.7%	mPFS: 8.0 mo (6.5, 10.9)	Martin et al. 2021
	1L, HER2+	Pertuzumab + trastuzumab + docetaxel	402	80%	mPFS: 18.5 mo	Baselga et al. 2012
	2L, HER2-	Everolimus + exemestane	485	12.6% (9.8, 15.9)	mPFS: 11.0 mo	Yardley et al. 2013
	2L, HER2+	Tucatinib + capecitabine + trastuzumab	320	40.6% (35.3, 46.0)	mPFS: 7.8 mo (7.5, 9.6)	Murthy et al. 2020
Sarcoma (soft tissue)	1L	Doxorubicin	251	18% (13.5, 23.1)	mPFS: 6.8 mo	Tap et al. 2020
	≥2L	Pazopanib	246	6%	mPFS: 4.6 mo	van der Graaf et al. 2012
Xanthogranuloma[c]	No standard					
	1L	Methotrexate + cytarabine	83	88% (includes multiple histiocytic diseases)	3-year EFS: 68.0%	Cao et al. 2020

Cancer Type	Line of Therapy	Treatment (Cancer Subtype)	N	Response Rate (%) (95% CI[a])	Time to Event Endpoints	Reference
Biliary tract cancers	1L	Gemcitabine + cisplatin	161	26%	mPFS: 8.0 mo 2L	Valle et al. 2010
	≥2L none supported by ESMO-recommended clinical trials					
Non-melanoma skin	No standard					
Esophagogastric	1L, HER2+	Trastuzumab + cisplatin + capecitabine OR 5-FU	294	47% (NR)	mDOR: 6.9 mo (6, 8)	Bang et al. 2010
	1L, HER2-	5-FU + irinotecan	45	40% (25.7, 54.3)	mPFS: 6.9 mo (5.5, 8.3)	Bouché et al. 2004
	2L	Ramucirumab + paclitaxel	330	28% (23, 33)	mDOR: 4.4 mo (2.8, 7.5)	Wilke et al. 2014
Brain[d]	2L	Temozolomide (anaplastic astrocytoma)	162	35% (NR)	mPFS: 5.4 mo (NR)	Yung et al. 1999
		Temozolomide (glioblastoma)	14 53	14% (NR) 15% (NR)	6-mo PFS: 57% mPFS: 11.0 mo (9.2, 12.9)	Perry et al. 2008 Weller et al. 2015

Abbreviations: 1L = first line; 2L = second line; 3L = third line; 5-FU = fluorouracil; CAPEOX = capecitabine + oxaliplatin; CI = confidence interval; EFS = event-free survival; ESMO = European Society for Medical Oncology; FOLFIRI = 5-FU + folinic acid + irinotecan; FOLFOX = folinic acid + 5-FU + oxaliplatin; HER2+/- = human epidermal growth factor receptor 2 positive/negative; mDOR = median duration of response; mDOT = median duration of treatment; mOS = median overall survival; mPFS = median progression-free survival; mTTP = median time to progression; N = number of participants in the analysis population; NA = not available; NCCN = National Comprehensive Cancer Network; NR = not reached.

a CIs are reported where available.

b A pooled analysis of the bevacizumab-vs-placebo-containing arms (FOLFOX-4 and bevacizumab + CAPEOX and bevacizumab vs FOLFOX-4 and placebo + XELOX plus placebo) comprised the main analysis. Overall, 699 patients comprised the bevacizumab-containing arms, and 701 patients comprised the placebo-containing arms.

c Xanthogranuloma is a subtype of histiocytosis. There are no NCCN-recommended standard-of-care therapies available for xanthogranuloma. If systemic therapy is needed, methotrexate + cytarabine are suggested for use according to EMSO histiocytosis guidelines.

d All studies related to the brain describe recurrent disease postradiation therapy (with or without chemo).

2.1.2. About the product

Selpercatinib is a first-in-class, small molecule inhibitor of RET which has been granted a conditional marketing authorisation on 11 February 2021.

As of today the approved indications are the monotherapy treatment of (1) adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor, (2) adults and adolescents 12 years and older with (a) advanced RET fusion-positive thyroid cancer who are

radioactive iodine-refractory (if radioactive iodine is appropriate) and (b) advanced RET-mutant medullary thyroid cancer (MTC).

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

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

The recommended dose of Retsevmo based on body weight is:

-Less than 50 kg: 120 mg twice daily.

-50 kg or greater: 160 mg twice daily.

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

Treatment should be continued until disease progression or unacceptable toxicity.

The CHMP adopted the following indication:Retsevmo as monotherapy is indicated for the treatment of adults with advanced *RET* fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted (see sections 4.4 and 5.1).

2.1.3. Development program

Evaluation of clinical safety and efficacy of selpercatinib in patients with *RET* fusion-positive tissue-agnostic solid tumours is based on the analysis of interim data from LIBRETTO-001 (LOXORET- 17001; J2G-OX-JZJA). LIBRETTO-001 is a global, multicohort, open-label, phase 1/2 study in adult and adolescent with advanced RET-altered tumours.

Table 2. Regulatory interactions in the EU for Retsevmo

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

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

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

2.1.4. General comments on compliance with GCP

Study LIBRETTO-001 was subject to independent audit by regulatory authorities. The audits performed as of 24 September 2021 are presented in Table 3.

Table 3. Clinical studies contained in this application that were inspected by regulatory authorities

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

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

The CHMP reviewed the observations reported following the GCP inspections and the actions taken in response to these observations and agreed that none of the observations is likely to have impacted the outcomes of the study.

2.2. Non-clinical aspects

No new non-clinical data, except for the ERA, have been submitted in this application.

2.2.1. Ecotoxicity/environmental risk assessment

Prevalence of Requested Indication

The current application requests that the indicated population be expanded to include patients with any solid cancers that have been characterized as having RET fusions without regard to cancer location or histology. The prevalence of "other cancers" was derived from the prevalence of all cancers in each EU member state using 3-year prevalence data (IARC, accessed 2022) adjusted by subtracting the prevalence of NSCLC, MTC, PTC and other thyroid cancers. The frequency of RET fusions in cancers other than NSCLC, MTC, PTC, other thyroid cancers and excluding blood and heme cancers was then used to refine the prevalence of indicated "other cancers."

Since the PECsurface water is greater than 0.01 µg·L-1, a Phase II risk assessment has been conducted.

Table 4. Environmental Risk Assessment for Selpercatinib: summary of main study results

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

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

					normalized to 10% organic carbon.

2.2.2. Discussion on non-clinical aspects

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

The Retsevmo (selpercatinib) ERA dossier submitted with this variation has been conducted for the histology-independent indication and the additional thyroid indication assessed in the context of variation II-21, in addition to the already approved indications.

Based on the prevalence data for these 5 indications by the WHO (IARC) in Europe, it appears that the highest value of PECsw 0.034 g/L is recorded in Cyprus and retained by the manufacturer.

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

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of selpercatinib.

Considering the above data, selpercatinib is not expected to pose a risk to the environment.

Taking into account the new indication (*RET* fusion-positive histology-independent solid tumours), selpercatinib does not appear to present a risk for aquatic organisms in the environment and is not classified as PBT or vPvB. The vP criterion is met for DT50 sediment and DT50 whole system.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

Table 5. Tabular overview of clinical studies

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

Abbreviations: 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; PK = pharmacokinetics; *RET* = REarranged during Transfection; RP2D = recommended Phase 2 dose; TTBR = time-to-best response.

[a] Patients treated in LIBRETTO-001 as of 24 September 2021 data cutoff.

Source: LIBRETTO-001 Interim CSR (24 September 2021 data cutoff).

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, two strengths of selpercatinib hard capsules, 40 and 80 mg, are available.

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 (EMEA/H/C/005375/0000). Please refer to section 5.2 of the current SmPC.

Variations EMEA/H/C/005375/II/0011 and 14 (for first-line treatment of NSCLC and MTC, respectively) and EMEA/H/C/005375/II/0021 submitted in parallel to variation EMEA/H/C/005375/II/0022 were based on the same interim PK data cut-off of 10 June 2021 from patients enrolled on the ongoing pivotal study LOXO-RET-17001, a phase 1/2 of oral selpercatinib in patients 12 years and older with advanced solid tumours, including RET fusion-positive tumours, RET-mutant MTC, and other tumours with RET activation.

The PK data provided in support of the current tissue-agnostic indication includes descriptive analysis of selpercatinib non-compartmental steady state PK data from adult patients of the claimed population enrolled in the pivotal study LOXO-RET-17001 and exploration of PK similarity across tumour types.

Pharmacokinetic in target population

PK data in Adult patients with tissue-agnostic solid tumour

PK data from study **LOXO-RET-17001** as of the data cut-off of 10 June 2021 were previously reported in the NSCLC, MTC and TC CSRs (please refer to EMEA/H/C/005375/II/0011; EMEA/H/C/005375/II/0014 and EMEA/H/C/005375/II/0021, respectively). Of the 757 patients with evaluable PK data, 34 patients had *RET* fusion-positive tissue-agnostic tumours.

Table 6 presents the systemic exposure of selpercatinib at steady-state ($AUC_{0\text{-}24h}$ and C_{max} at C1D8) for patients with cancer by tumour types (NSCLC, MTC and tissue-agnostic solid tumours) taking 160 mg selpercatinib BID. Figure 1 presents the associated box-plots to visualize the PK parameters distribution by tumour types.

Table 6. Steady-state (C1D8) PK parameters of selpercatinib in patients with cancer dosed 160 mg BID

	MTC		NSCLC (Including Asian Patients)		NSCLC (Excluding Asian Patients)		Tissue-Agnostic	
	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (h*ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (h*ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (h*ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (h*ng/mL)
N	278	275	291	283	156	149	34	31
GM	2760	46600	3400	60200	2960	50700	2710	44300
GCV%	53	55	48	52	48	53	53	57
90% CI	1317, 5349	22581, 97778	1575, 6565	26816, 123975	1435, 5203	22159, 95188	1133, 5243	19076, 100589

Abbreviations: AUC0-24 = area under the plasma concentration-time curve from time 0 to 24 hours; BID = twice daily; CI = confidence interval; Cmax = maximum plasma concentration; CV = coefficient of variation; N = number of samples; GM = geometric mean; MTC = medullary thyroid cancer; NSCLC= non-small cell lung cancer.

Sources: Data available from 09 May 2017 to 10 June 2021

Figure 1. Boxplots of plasma selpercatinib Cmax and AUC0-24 following selpercatinib 160 mg BID administrations (C1D8) in patients with cancer excluding Asian patients

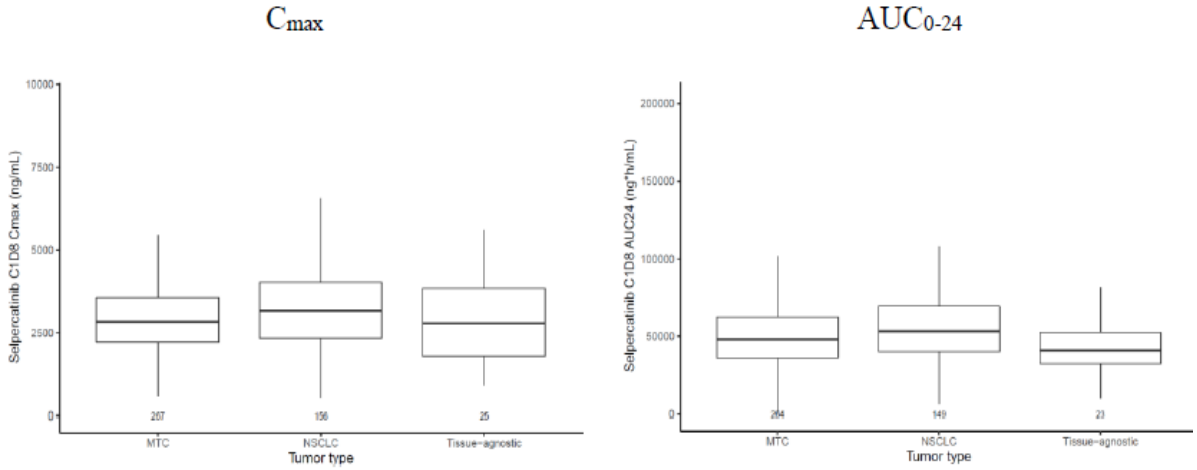
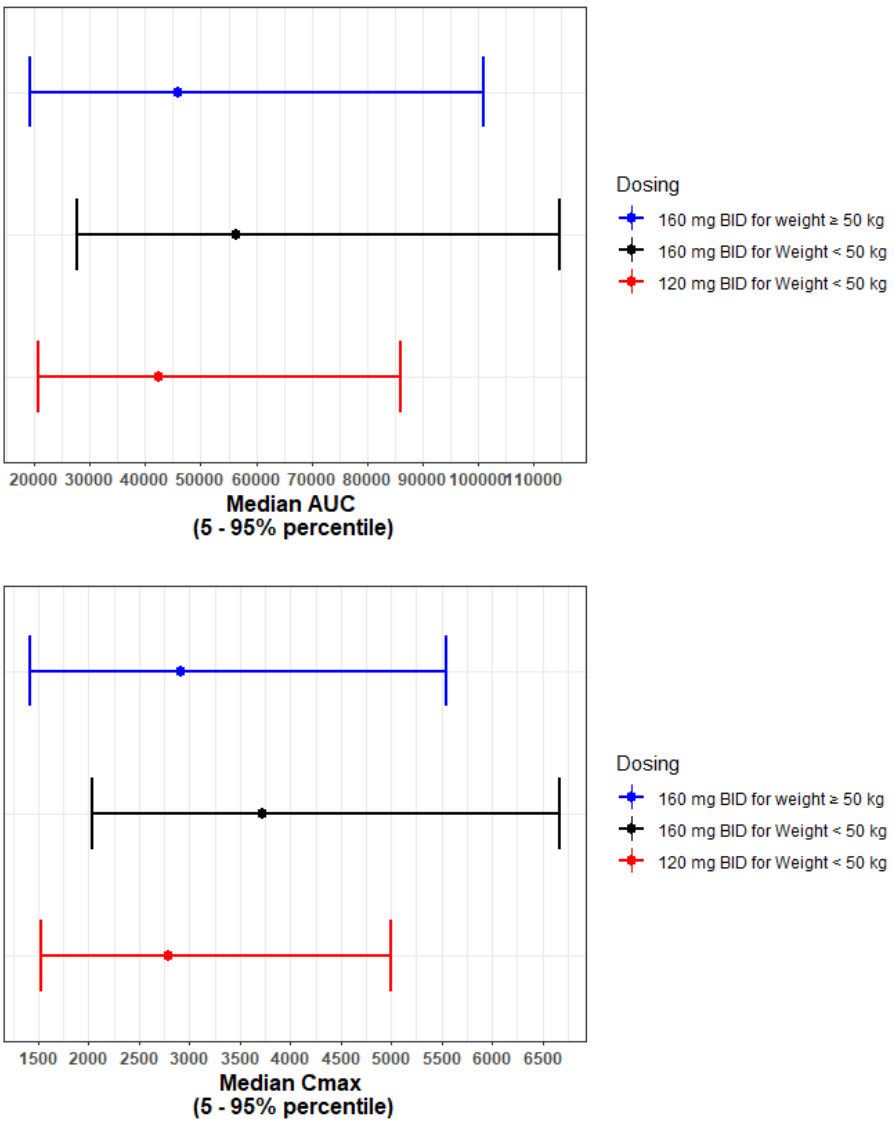


Figure 2: Simulated steady-state AUC and Cmax by weight and dosing



Abbreviations: AUC = area under the plasma concentration-time curve; BID = twice daily; Cmax = maximum plasma concentration.

2.3.3. PK/PD modelling

No new data was submitted in this application.

2.3.4. Discussion on clinical pharmacology

Based on the noncompartmental (NCA) approach, new PK data in the target population issued from the pivotal study LOXO-RET-17001 (cut-off date of 10 June 2021, N=34) were provided. Using the NCA approach, the observed systemic exposure on selpercatinib at steady-state (Cmax = 2710 ng/mL and AUC0-24h = 44300 ng.h/mL) were overall consistent with the known PK in approved NSCLC, TC and MTC populations.

In order to obtain PK information regarding the systemic exposure in patients with body weight less than 50 kg using the 120 mg BID dosing regimen, the MAH provided Pop-PK model-based simulations that showed similar exposures (median steady state AUC and median Cmax) in patients weighing above 50 kg with 160 mg BID dosage and patients weighing below 50 kg with 120 mg BID dosage irrespective of tumour types.

Simulations of patients with all tumour types dosed 160 mg BID showed that pharmacokinetic exposure parameters overlapped (median steady state AUC and median Cmax) between the different populations.

Therefore, it is agreed that the same weight-based dose regimen previously approved for patients with NSCLC and TC is considered appropriate for the tissue-agnostic indication.

2.3.5. Conclusions on clinical pharmacology

No significant difference in PKs characteristics of selpercatinib was observed in patients with tissue-agnostic solid tumours compared to patients with NSCLC, TC and MTC already approved. Therefore, from a PK perspective, the claim to extend selpercatinib indication to adult patients with RET fusion-positive tissue-agnostic solid tumours is accepted.

2.4. Clinical efficacy

2.4.1. Main study

LIBRETTO-001 A Phase 1/2 Study assessing selpercatinib in Patients with Advanced Solid Tumours, Including *RET* Fusion-Positive Solid Tumours, Medullary Thyroid Cancer, and Other Tumours with *RET* Activation.

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

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

- *advanced RET fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor (*EMEA/H/C/005375/0000 and EMEA/H/C/005375/II/0011)

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

- *advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate (*EMEA/H/C/005375/0000 and EMEA/H/C/005375/II/0021)

– *advanced RET-mutant medullary thyroid cancer (MTC) (*EMEA/H/C/005375/0000 and EMEA/H/C/005375/II/0014)

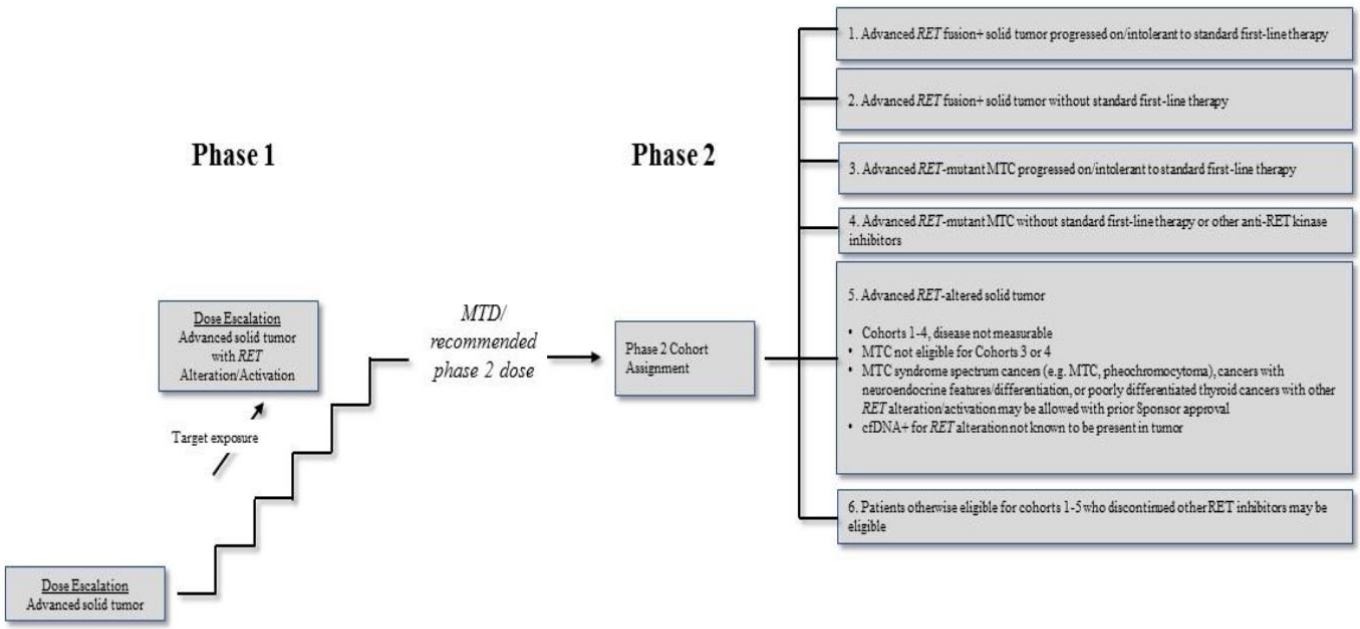
This is an ongoing open-label, multicenter, multi-country study in patients at least 12 years old with advanced solid tumours.

The study includes 2 parts:

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

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

Table 7. Study design of study LIBRETTO-001 as of Protocol Version 9.0



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

Methods

Study participants

Eligibility criteria at the time of this interim report remain the same as specified in the previous CSR (15 June 2021 data cut-off, as version 9.0 of the protocol was the ongoing version at the data cut-off). Main selection criteria are summarized below.

Inclusion criteria for Phase 1

- Patients with a locally advanced or metastatic solid tumour who
  - have progressed on or are intolerant to standard therapy, or
  - no standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or
  - decline standard therapy

- have measurable or nonmeasurable disease as determined by RECIST 1.1 or RANO as appropriate to tumour type
- are at least 18 years of age (or age 12 if allowed by local regulations)
- have an ECOG performance status score of 0, 1, or 2, and
- have a life expectancy of at least 3 months.

Inclusion criteria for Phase 2

1. Inclusion criteria are the same as for Phase 1, with the following modifications:
    - evidence of *RET* gene alteration in tumour and/or blood
    - Cohorts 1 and 3: failed or intolerant to standard of care, and
    - Cohorts 2 and 4: without prior standard first-line therapy.

Table 8. Standard of care therapy for cohort 1-4

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

Note: Standard of Care may vary by country

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

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

4. Cohort 4: radiographic PD within the previous 14 months.

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

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

Note: Examples of RET inhibitors may include TPX0046, pralsetinib (BLU-667), or BOS172739.

Exclusion criteria

Patients meeting any of the following criteria are to be excluded from study participation:

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

2. Cohorts 1-5: prior treatment with a selective RET inhibitor(s) (including investigational selective RET inhibitor[s]).

Notes: Patients otherwise eligible for Cohorts 1-5 who discontinued another selective RET inhibitor may be eligible for Phase 2 Cohort 6 with prior Sponsor approval.

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 ongoing Phase 2 dose-expansion phase of the study.

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

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

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

Objectives

The primary objective of the Phase 1 portion of LIBRETTO-001 was to determine the maximum tolerated dose and RP2D of selpercatinib. A dose of 160 mg BID was selected for Phase 2.

Outcomes/endpoints

Table 9. Objectives and endpoints

Objectives	Endpoints
Primary	
• Assess the antitumor activity of selpercatinib in patients with *RET* fusion–positive cancer other than NSCLC and thyroid cancer	• ORR based on IRC assessment using RECIST 1.1
Secondary	
• Assess the antitumor activity of selpercatinib in patients with *RET* fusion–positive cancer other than NSCLC and thyroid cancer	• ORR based on investigator assessment using RECIST 1.1 • TTR, TTBR, DOR, CBR • PFS • OS
• Determine the safety profile and tolerability of selpercatinib in patients with *RET* fusion–positive cancer other than NSCLC and thyroid cancer	• Safety per CTCAE (including but not limited to): frequency and severity of TEAEs, SAEs, deaths, and clinical laboratory abnormalities

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; CBR = clinical benefit rate; DOR = duration of response; IRC = independent review committee; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = severe adverse event; TEAE = treatment-emergent adverse event; TTBR = time to best response; TTR = time to response.

• OS following initiation of selpercatinib	
• 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

The planned sample size is estimated to provide approximately 79% power to reject the null hypothesis that the true ORR is ≤20% with a 2-sided alpha of 5% (Clopper and Pearson 1934).

Ruling out a lower limit of 20% for ORR is considered clinically meaningful comparing to available treatment options.

Assuming the minimum sample size of 32 patients, the following scenarios have been considered.

- If the true ORR is 43%, the sample size of 32 patients will provide approximately 79% power to reject the null hypothesis that the true ORR is ≤20%.
- If the true ORR is 45%, the sample size of 32 patients will provide approximately 85% power to reject the null hypothesis that the true ORR is ≤20%.

Looking at individual tumour types, a subgroup sample size of 10 patients was considered for the following scenarios:

- If the true ORR is 40%, the sample size of 10 patients will provide approximately 62%power to achieve a lower boundary of a 95% CI that exceeds 10%.
- If the true ORR is 40%, the sample size of 10 patients will provide approximately 83%power to achieve a lower boundary of a 95% CI that exceeds 5%.

In each rare tumour type with a low prevalence, a limited number of patients will be enrolled in subgroups based on tumour types. Table 9 shows different scenarios for probability that at least one response is observed when the true ORR is 40%.

Table 10. Probability of observing at least one response

Sample Size	Probability of at least One Response Observed
2	0.64
3	0.78
4	0.87
5	0.92

Randomisation

Not applicable.

Blinding (masking)

This is an open-label study.

Statistical methods

This interim CSR follows the SAP (JZJA Tissue-agnostic SAP Version 2.0) prepared to

- document and specify the statistical methods used for analyses to demonstrate the effectiveness and the safety of selpercatinib in patients with RET fusion-positive histology-independent solid tumors, and
- support a potential histology-independent indication for selpercatinib for RET fusion-positive solid tumors.

Patients from the Phase 1 and Phase 2 portions of LIBRETTO-001 were included in analysis sets evaluating efficacy in specific tumour types. In addition to patients previously included in the original new drug application (i.e., patients with advanced or metastatic *RET*-fusion NSCLC and thyroid cancer, as well as *RET*-mutant MTC), patients with *RET* fusion-positive solid tumours other than NSCLC or thyroid cancer were enrolled per protocol if they had progressed on or were intolerant to the standard-of-care therapies.

Measures to Minimise Bias

This study included an IRC for efficacy assessments in addition to the Investigator assessments. The primary radiography imaging files from LIBRETTO-001 were sent to a third-party vendor for central review. These measures aimed to minimise bias and support data consistency.

Statistical Analysis Plan

The protocol and the JZJA Tissue-agnostic SAP Version 2.0 provide the planned analyses for the study, comparisons, statistical tests, and determination of sample size.

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

Analysis Sets

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

The goal of the arrangement of these various datasets was to

- maximise 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

    - *Safety Analysis Set for RET Fusion-Positive Tissue-Agnostic Solid Tumours*

The Safety Analysis Set (N=45) included patients with *RET* fusion-positive tissue-agnostic solid tumours who were enrolled and received at least 1 dose of selpercatinib as of the data cut-off date of 24 September 2021, and included 55 patients as of 13 January 2023 DCO

    - *Efficacy Analysis Set for RET Fusion-Positive Tissue-Agnostic Solid Tumours*

The Tissue-agnostic Efficacy Analysis Set (N=41) included all patients with *RET* fusion-positive Tissue-agnostic solid tumours who had achieved at least 6 months of potential follow-up time from the first dose of selpercatinib and included 52 patients as of 13 January 2023 DCO.

In the interim report,

- efficacy was analysed for all patients who had achieved at least 6 months of potential follow-up from the first dose, and
- all responders were followed for 6 months post initial response unless they progressed or died earlier.

Changes in Planned Analyses Prior to Unblinding or Database Lock

This interim CSR follows the SAP prepared to

- document and specify the statistical methods used for analyses to demonstrate the effectiveness and the safety of selpercatinib in patients with *RET* fusion-positive histology-independent solid tumours, and
- support a potential tissue-agnostic indication for selpercatinib for *RET* fusion-positive solid tumours.

There were no changes in the planned analyses for the study which are described in the SAP Version 2.0.

Sensitivity Analyses

Sensitivity analyses for the ORR based on RECIST 1.1 by the IRC will be conducted as defined below:

- repeating the main ORR analysis for patients who received at least one dose of selpercatinib of 160 mg twice a day (BID)
- excluding patients with only non-measurable disease by the IRC from the efficacy analysis set (unless patients achieved a CR)

Results

Participant flow

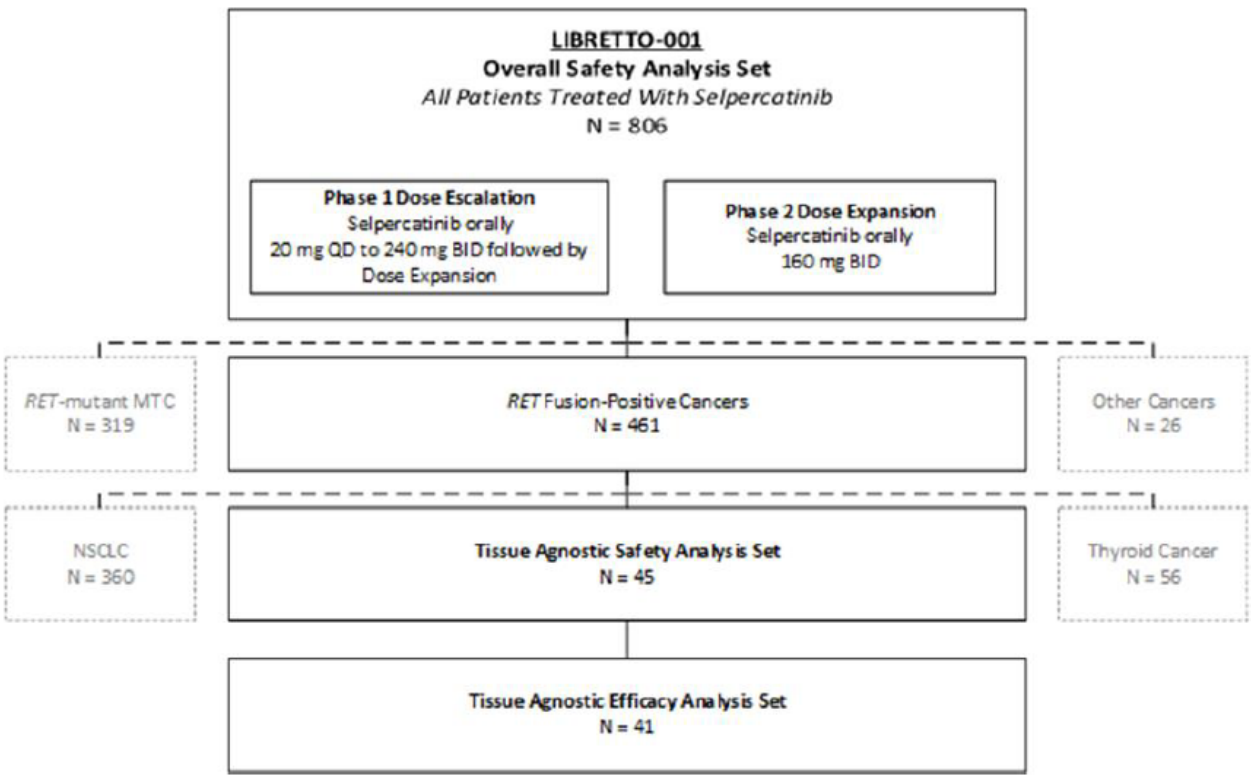
The initial data provided were based on a data cut-off date of 24 September 2021. During the procedure, updated data were provided. As of the latest data cut-off date (13 January 2023), 968 patients were screened. Of these, 131 patients were screen failures. Reasons for screen failures are presented in Table 10. As a result, the Overall Safety Analysis Set consisted of 837 patients who were treated with at least 1 dose of selpercatinib.

Table 11. Screen Failures All Screened Patients (DCO 13 January 2023)

Characteristic	Total
Subjects Screened (n)	968
Subjects Treated (n, %)*	837 (86.5)
Subjects with Screen Failure (n, %)*	131 (13.5)
Reason for Screen Failure (n, %)**	
DID NOT SATISFY ALL INCLUSION OR EXCLUSION CRITERIA	92 (70.2)
ADVERSE EVENT	11 (8.4)
WITHDRAWAL OF CONSENT	10 (7.6)
INVESTIGATOR DECISION	3 (2.3)
DEATH	2 (1.5)
OTHER	13 (9.9)

*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.
Patient 115-006 is the only early-
stage NSCLC patient treated with selpercatinib in neoadjuvant setting.
Patient was analyzed separately and will be reported in a separate clinical study report.

Table 12. Flow diagram depicting histology-independent analysis sets LIBRETTO-001 (DCO 24 September 2021)



Abbreviations: BID = twice daily; MTC = medullary thyroid cancer; N = number of patients in the population; NSCLC = non-small cell lung cancer; QD = once daily; *RET* = Rearranged during Transfection.
Note: Dashes indicate patients not included in any tissue-agnostic dataset.
Data cutoff date: 24 September 2021.

Table 13 Patient Distribution by Study Phase and Cohort

	Phase 1		Phase 2	
Cohort	Dose Escalation/ Starting Dose	Dose Expansion at 160 mg BID	Included in Efficacy Eligible Set 24 September 2021 Data Cut-off	Additional Patients in Efficacy Eligible Set 13 January 2023 Data Cut-off
Cohort 1	1/ 80 mg BID 1/ 120 mg BID 1/ 160 mg BID	2	25	8
Cohort 2			1	1
Cohort 5			10	2

Eligible patients are defined as patients treated on or before 13-JUL-2022.

Tissue-agnostic Efficacy Analysis Set

As of 24 September 2021, 18 (43.9%) patients were still on treatment. Disease progression (31.7%) was the most common reason for treatment discontinuation. The number of patients who discontinued treatment due to a TEAE was low (9.8%).

Twenty-one patients (46.7%) were still on treatment at the cut-off date. The most common reason for treatment discontinuation was disease progression (13 patients [28.9%]), followed by TEAEs (4 patients [8.9%]).

Table 14. Summary of disposition Tissue-agnostic Safety and Efficacy Analysis Sets (DCO 24 September 2021)

	***RET* Fusion-Positive Tissue-agnostic Solid Tumors**	
Study Disposition	**Safety Analysis Set N=45 n (%)**	**Efficacy Analysis Set N=41 n (%)**
Treatment status		
Discontinued	24 (53.3)	23 (56.1)
On treatment	21 (46.7)	18 (43.9)
Reason for treatment discontinuation		
Disease progression	13 (28.9)	13 (31.7)
Adverse event	4 (8.9)	4 (9.8)
Withdrawal of consent	2 (4.4)	2 (4.9)
Death	2 (4.4)	2 (4.9)
Other	2 (4.4)	1 (2.4)
Lost to follow-up	1 (2.2)	1 (2.4)
Study status		
Discontinued	22 (48.9)	21 (51.2)
On study	23 (51.1)	20 (48.8)
Reasons for study discontinuation		
Withdrawal of consent	2 (4.4)	2 (4.9)
Lost to follow-up	1 (2.2)	1 (2.4)
Death	19 (42.2)	18 (43.9)

Abbreviations: N = number of patients in analyses set; n = number of patients in the specific category; *RET* = Rearranged during Transfection.

Table 15. Summary of disposition Tissue-agnostic Safety and Efficacy Analysis Sets (DCO 13 January 2023)

RET Fusion-Positive Tissue-Agnostic Solid Tumours (N = 52)	
Study Disposition	**n (%)**
Treatment status	
Discontinued	36 (69.2)
On treatment	16 (30.8)
Reason for treatment discontinuation	
Progressive disease	23 (44.2)
Adverse event	5 (9.6)
Withdrawal of consent	3 (5.8)
Death	1 (1.9)
Other	3 (5.8)
Lost to follow-up	1 (1.9)
Study status	
Discontinued	33 (63.5)
On study	19 (36.5)
Reason for study discontinuation	
Death	30 (57.7)
Withdrawal of consent	2 (3.8)
Lost to follow-up	1 (1.9)

Abbreviations: n = number of patients per category; N = number of patients in the population; RET = REarranged during Transfection.

Data cutoff date: 13 January 2023

On 05 February 2024 (no formal DCO), 74 patients with RET-fusion other than NSCLC and MTC were included in LIBRETTO-001.

Recruitment

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

Study initiation date (first participant first visit): 9 May 2017.

Data cut-off date for interim analysis: 24 September 2021.

Updated efficacy data were provided during the procedure, with data cut-off date: 13 January 2023.

Conduct of the study

The version 9 of the protocol was the ongoing version at the data cut off 24 September 2021 was version 9. It is the same version than for the previous submission.

Table 16. Summary of Important Protocol deviations Tissue-agnostic Safety Analysis Set (DCO 24 September 2021)

Category	*RET* Fusion-Positive Tissue-agnostic Solid Tumors (N=45) n (%)
Patients with major protocol deviations	11 (24.4)
Investigational product	3 (6.7)
Study procedures	3 (6.7)
SAE reporting	2 (4.4)
Restricted concomitant medication change	2 (4.4)
Inclusion criteria	2 (4.4)
Withdrawal criteria	1 (2.2)

Abbreviations: N = number of patients; n = number of patients in the specific category; *RET* = Rearranged during Transfection; SAE = serious adverse event.
Date cutoff date: 24 September 2021.

Overall, at DCO 13 Jan 2023, 21 CSR-reportable protocol deviations occurred in 13 patients with tissue-agnostic tumour, of which,

- 6 were missed procedures in 3 patients,
- 3 were SAEs in 3 separate patients that were reported after 24 hours of site awareness of the event
- 6 were study-drug-related PDs in 4 patients
- 1 patient did not discontinue when met discontinuation criteria (efficacy data by the investigator was censored at the time the patient met discontinuation criteria)
- 2 were restricted concomitant medications in 2 separate patients
- 3 were inclusion criteria

Baseline data

Demographics

Table 17. Summary of Demographics Tissue-agnostic Safety Analysis Set (DCO 24 September 2021)

Category	*RET* Fusion-Positive Tissue-agnostic Solid Tumors (N=45)
Age (years), n	
Median (range)	53 (21-85)
Overall age group, n (%)	
18-44 years	15 (33.3)
45-64 years	17 (37.8)
65-74 years	9 (20.0)
75-84 years	3 (6.7)
≥85 years	1 (2.2)
Sex, n (%)	
Male	22 (48.9)
Female	23 (51.1)
Race, n (%)	
White	31 (68.9)
Black or African American	2 (4.4)
Asian	11 (24.4)
Native Hawaiian or other Pacific Islander	1 (2.2)
Ethnicity, n (%)	
Hispanic or Latino	3 (6.7)
Not Hispanic or Latino	41 (91.1)
Not reported	1 (2.2)
Body weight (kg)	
N	45
Median	64.80
Range	40.6-105.0
Baseline ECOG, n (%)	
0	15 (33.3)
1	27 (60.0)
2	3 (6.7)

Table 18. Summary of Demographics Tissue-agnostic Efficacy Eligible Population (DCO 13 January 2023)

	RET Fusion Colon (N=13)	RET Fusion Pancreas (N=13)	Total RET Fusion Non Lung/Thyroid (N=52)
Sex (n, %)			
Male	7 (53.8)	6 (46.2)	25 (48.1)
Female	6 (46.2)	7 (53.8)	27 (51.9)
Race (n, %)			
White	7 (53.8)	11 (84.6)	35 (67.3)
Black or African American	2 (15.4)	0 (0.0)	3 (5.8)
Asian	3 (23.1)	2 (15.4)	13 (25.0)
Native Hawaiian or Other Pacific Islander	1 (7.7)	0 (0.0)	1 (1.9)
Ethnicity (n, %)			
Hispanic or Latino	1 (7.7)	0 (0.0)	3 (5.8)
Non Hispanic or Latino	12 (92.3)	13 (100.0)	48 (92.3)
Missing	0 (0.0)	0 (0.0)	1 (1.9)
Age Group (n, %)			
18 to <45 years	1 (7.7)	5 (38.5)	16 (30.8)
45 to <65 years	7 (53.8)	7 (53.8)	21 (40.4)
65 to <75 years	3 (23.1)	1 (7.7)	11 (21.2)
75 to <85 years	1 (7.7)	0 (0.0)	3 (5.8)
85+ years	1 (7.7)	0 (0.0)	1 (1.9)

	RET Fusion Colon (N=13)	RET Fusion Pancreas (N=13)	Total RET Fusion Non Lung/Thyroid (N=52)
Age (yrs)			
n	13	13	52
Mean (SD)	60.1 (13.73)	49.3 (11.23)	53.1 (15.60)
Median	60.0	50.0	54.0
Min-Max	32-85	31-65	21-85
Height (cm)			
n	12	13	50
Mean (SD)	169.4 (12.52)	165.8 (9.31)	167.7 (10.51)
Median	170.0	166.0	166.5
Min-Max	153-196	152-181	152-196
Weight (kg)			
n	13	13	52
Mean (SD)	71.68 (18.079)	66.93 (11.796)	67.70 (15.885)
Median	69.40	61.70	66.50
Min-Max	40.8-105.0	48.1-85.5	40.6-105.0

	RET Fusion Colon (N=13)	RET Fusion Pancreas (N=13)	Total RET Fusion Non Lung/Thyroid (N=52)
Body Mass Index (kg/m^2)			
n	12	13	50
Mean (SD)	24.94 (5.040)	24.38 (3.966)	24.06 (4.520)
Median	23.89	25.03	24.12
Min-Max	17.4-33.2	19.1-31.0	16.6-33.2
ECOG Performance Status (n, %)			
0	3 (23.1)	4 (30.8)	16 (30.8)
1	8 (61.5)	8 (61.5)	32 (61.5)
2	2 (15.4)	1 (7.7)	4 (7.7)
Smoking Status (n, %)			
Current Smoker	0 (0.0)	0 (0.0)	2 (3.8)
Former Smoker	7 (53.8)	1 (7.7)	15 (28.8)
Never A Smoker	6 (46.2)	11 (84.6)	34 (65.4)
Missing	0 (0.0)	1 (7.7)	1 (1.9)

Cutoff Date: 2023-01-13.
Efficacy eligible subjects are defined as the subjects whose first dose date is on or before 2022-07-13.
Percentage is calculated using the number of patients in the column heading as the denominator.
Abbreviations: SD = Standard Deviation.

Disease characteristics

Patients in LIBRETTO-001 with *RET* fusion-positive tissue-agnostic solid tumours represented 14 unique tumour types (Table 18). The most common tumour types were pancreatic, colorectal, and salivary gland.

Table 19. Baseline Disease Characteristics Tissue-agnostic Safety Analysis Set (DCO 24 September 2021)

	RET Fusion-Positive Tissue-agnostic Solid Tumors N=45
Primary diagnosis, n (%)	
Pancreatic	12 (26.7)
Colon	10 (22.2)
Salivary[a]	4 (8.9)
Unknown primary	3 (6.7)
Sarcoma	3 (6.7)
Breast	2 (4.4)
Xanthogranuloma[b]	2 (4.4)
Cholangiocarcinoma	2 (4.4)
Carcinoma of the skin	2 (4.4)
Ovarian	1 (2.2)
Carcinoid[c]	1 (2.2)
Small intestine	1 (2.2)
Pulmonary carcinosarcoma	1 (2.2)
Rectal neuroendocrine	1 (2.2)
Stage at initial diagnosis, n (%)	
Stage IIB	1 (2.2)
Stage III	3 (6.7)
Stage IV	38 (84.4)
Missing	3 (6.7)
Months since initial diagnosis	
Mean (SD)	24.3 (33.9)
Median	15.6
Min-max	1.7-213.2
History of metastatic disease, n (%)	
Yes	43 (95.6)
No	2 (4.4)
Measurable disease (by Investigator assessment)	40 (88.9)
Measurable disease (by IRC assessment)	36 (8.0)

Abbreviations: Max = maximum; Min = minimum; N = number of patients in the population; n = number of patients per category; *RET* = REarranged during Transfection; SD = standard deviation.

Diagnosis of primary tumor type:

[a] Salivary gland adenocarcinoma (1) and cancer of parotid gland (3).

[b] Disseminated cutaneous juvenile xanthogranulomatosis.

[c] Atypical carcinoid tumor.

Data cutoff date: 24 September 2021.

Baseline disease characteristics (DCO 13 January 2023)

	N	
	N as of September 2021	N as of January 2023
Tissue-Agnostic Efficacy Population	41	52
Pancreatic	11	13
Colorectal	10	13
Salivary	4	4
Cholangiocarcinoma	1	3
Unknown primary	3	3
Sarcoma	2	3
Breast	2	2
Xanthogranuloma	2	2
Carcinoma of the skin	1	2
Carcinoid	1	1
Ovarian	1	1
Small intestine	1	1
Pulmonary carcinosarcoma	1	1
Rectal neuroendocrine	1	1
Neuroendocrine	-	1
Small cell lung cancer	-	1

Efficacy-eligible patients are defined as the patients whose first dose date was on or before 13 January 2023.

RET alteration status

Table 20. Baseline Disease Characteristics – *RET* Fusion Status Tissue-agnostic Safety Analysis Set (DCO 24 September 2021)

RET Alteration Type	*RET* Fusion-Positive Tissue-agnostic Solid Tumors	
	Safety Analysis Set (N=45) n (%)	Efficacy Analysis Set (N=41) n (%)
Fusion	45 (100.0)	41 (100.0)
NCOA4	17 (37.8)	16 (39.0)
CCDC6	7 (15.6)	6 (14.6)
KIF5B	4 (8.9)	4 (9.8)
RET gene rearrangement	3 (6.7)	2 (4.9)
Other[a]	14 (31.1)	13 (31.7)
Molecular assay type		
NGS on tumor	40 (88.9)	36 (87.8)
NGS on blood or plasma	3 (6.7)	3 (7.3)
FISH	1 (2.2)	1 (2.4)
Other[b]	1 (2.2)	1 (2.4)

Abbreviations: N = number of patients; n = number of patients in the specific category; NGS = next-generation sequencing; *RET* = REarranged during Transfection.

[a] Additional fusion partners: ETV6 (n=2), CGNL1 (n=1), ERC1 (n=1), KIAA1217 (n=1), GPHN (n=1), PRKAR1A (n=1), SPECC1L (n=1), TFG (n=1), GOLGA5 (n=1), RASAL2 (n=1), TAF3 (n=1), TRIM24 (n=1), TRIM33 (n=1), and unknown (n=1).

[b] Other molecular assay type is Liquid Biopsy using NGS.

Data cutoff date: 24 September 2021.

Table 21: Summary of Molecular Pathology Test Tissue-Agnostic Efficacy-Eligible Population (DCO 13 January 2023)

Characteristics	RET Fusion Colon (N=13)	RET Fusion Pancreas (N=13)	Total RET Fusion Non Lung/Thyroid Solid Tumors (N=52)
Test Methods (n, %)			
NGS	13 (100.0)	13 (100.0)	50 (96.2)
FISH	0 (0.0)	0 (0.0)	1 (1.9)
Unknown	0 (0.0)	0 (0.0)	1 (1.9)
Fusion Partner Identified (n, %)			
NCOA4	10 (76.9)	2 (15.4)	18 (34.6)
CCDC6	3 (23.1)	2 (15.4)	9 (17.3)
TRIM24	0 (0.0)	2 (15.4)	2 (3.8)
CGNL1	0 (0.0)	1 (7.7)	1 (1.9)
ERC1	0 (0.0)	1 (7.7)	1 (1.9)
GPHN	0 (0.0)	1 (7.7)	1 (1.9)
PRKAR1A	0 (0.0)	1 (7.7)	1 (1.9)
SATB1	0 (0.0)	1 (7.7)	1 (1.9)
SPECC1L	0 (0.0)	1 (7.7)	1 (1.9)
TFG	0 (0.0)	1 (7.7)	1 (1.9)
ETV6	0 (0.0)	0 (0.0)	2 (3.8)
GOLGA5	0 (0.0)	0 (0.0)	1 (1.9)
KANK1	0 (0.0)	0 (0.0)	1 (1.9)
KIAA1217	0 (0.0)	0 (0.0)	1 (1.9)
KIF5B	0 (0.0)	0 (0.0)	6 (11.5)
RAP1GAP2	0 (0.0)	0 (0.0)	1 (1.9)
RASAL2	0 (0.0)	0 (0.0)	1 (1.9)
TAF3	0 (0.0)	0 (0.0)	1 (1.9)
TRIM33	0 (0.0)	0 (0.0)	1 (1.9)
Unknown	0 (0.0)	0 (0.0)	1 (1.9)
In-Frame Fusion (n, %) [1]			
Yes	7 (53.8)	7 (53.8)	28 (53.8)
No	6 (46.2)	6 (46.2)	24 (46.2)
Presence of Concomitant Oncogenic Driver Mutation other than RET (n, %)			
Yes	1 (7.7)	0 (0.0)	1 (1.9)
No	12 (92.3)	13 (100.0)	51 (98.1)
Oncogenic Driver Identified			
KRAS A146V (0.2%)	1 (7.7)	0 (0.0)	1 (1.9)

Cutoff Date: 2023-01-13
Efficacy eligible subjects are defined as the subjects whose first dose date is on or before 2022-07-13.
This summary table is based on individual molecular pathology test, not based on EDC data.
[1] In-frame RET gene fusion status was counted as a 'yes' if the molecular report noted the fusion was in-frame or if DNA breakpoints were reported such that in-frame status could be determined via genomic analysis. Based on this definition, certain tests(e.g. FoundationOne) that do not explicitly state frame status were scored by the Sponsor as 'no' despite the fact that these fusions were likely evaluated for frame status prior to report generation.

Prior cancer treatments

Of the 41 patients in the Tissue-agnostic Efficacy Analysis Set, 37 patients (90.2%) received prior systemic therapy as required per protocol, with a median of 2 prior lines of therapy (range: 0 to 9):

- 9 (22.0%) received 1 prior line of therapy
- 15 (36.6%) received 2 prior lines of therapy, and 13 (31.7%) received 3 or more lines of prior treatment.

Table 22. Prior Cancer Treatment Tissue-agnostic Safety and Efficacy Analysis Set (DCO 24 September 2021)

	RET Fusion-Positive Tissue-agnostic Solid Tumors	
Analysis Set	Safety Analysis Set (N=45) n (%)	Efficacy Analysis Set (N=41) n (%)
Prior cancer treatments, n (%)[a]		
Systemic therapy	41 (91.1)	37 (90.2)
Chemotherapy	37 (82.2)	33 (80.5)
Immunotherapy	7 (15.6)	7 (17.1)
MKI	5 (11.1)	4 (9.8)
Other[b]	15 (33.3)	15 (36.6)
Surgery	27 (60.0)	24 (58.5)
Radiotherapy	17 (37.8)	15 (36.6)
Number of prior systemic regimens, n (%)		
0	4 (8.9)	4 (9.8)
1	10 (22.2)	9 (22.0)
2	17 (37.8)	15 (36.6)
3 or more	14 (31.1)	13 (31.7)
Number of prior systemic regimens		
Median	2.00	2.00
Range	0.0-9.0	0.0-9.0

Abbreviations: EGFR = epidermal growth factor receptor; MKI = multikinase inhibitor; mTOR = mammalian target of rapamycin; N = number of patients in the population; n = number of patients per category; *RET* = REarranged during Transfection; VEGF = vascular endothelial growth factor; VEFGR = VEGF receptor.

[a] Patients may be counted in more than 1 row.

[b] Other included mTOR, EGFR, VEGF/VEGFR inhibitors, hormonal therapy, and other systemic therapy.

Data cutoff date: 24 September 2021.

At the time of study enrolment, 4 patients were treatment naive:

- 2 patients with cancers of unknown primary origin, and
- 2 patients with xanthogranuloma.

These 4 treatment-naive patients were deemed to have no satisfactory standard-of-care therapeutic options at the time of study enrolment. For patients with cancers of unknown primary origin, NCCN guidelines recommend next-generation sequencing testing and targeted therapy if an actionable finding is identified rather than empirical chemotherapy. There is currently no standard of care for patients with advanced xanthogranuloma.

Update at DCO 13 January 2023:

Forty-seven patients (90.4%) received prior systemic therapy, with a median of 2 prior systemic therapies (range 0 to 9) and 28.8% received 3 or more prior systemic therapies.

Concomitant therapy

The most frequently used therapeutic classes of concomitant medications in the *RET* fusion positive Tissue-agnostic Safety Analysis Set included natural opium alkalides (51.1%), serotonin (5HT3) antagonists (42.2%), anilides (40.0%), and glucocorticoids (40.0%).

Numbers analysed

The Tissue-agnostic Efficacy Analysis Set (N=41) included all patients with *RET* fusion-positive Tissue-agnostic solid tumours who had achieved at least 6 months of potential follow-up time from the first dose of selpercatinib.

At the time of data cut-off (24 September 2021), the 18 responders (based on Investigator assessment) were followed for at least 6 months unless a response follow-up was discontinued:

- 13 were followed for at least 6 months from the time of initial response
- 2 had disease progression
- 1 died
- 1 had targeted lesion resection and became not evaluable for a response follow-up per RECIST, and
- 1 withdrew consent

At DCO2 (13 January 2023), out of 52 patients, the 23 responders (based on Investigator assessment) were followed for at least 6 months unless a response follow-up was discontinued:

- 6 had disease progression
- 4 died
- 9 were alive without documented disease progression
- 1 had targeted lesion resection and became not evaluable for a response follow-up per RECIST, and
- 1 withdrew consent
- 2 died or had documented pd after missing two or more consecutive visits

Outcomes and estimation

ORR and DoR

Table 23. Objective Response Rate, Best Overall Response, Duration of Response, Disease Control Rate, and Clinical Benefit Rate (DCO 24 September 2021)

RET Fusion-Positive Tissue-agnostic Solid Tumors N=41		
	IRC Assessment	Investigator Assessment
Objective response rate[a,b]		
n (%)	18 (43.9)	18 (43.9)
95% CI	(28.5, 60.3)	(28.5, 60.3)
Best overall response, n (%)		
CR	2 (4.9)	2 (4.9)
PR	16 (39.0)	16 (39.0)
SD	14 (34.1)	13 (31.7)
SD16+[c]	8 (19.5)	8 (19.5)
PD	3 (7.3)	7 (17.1)
Not evaluable[d]	6 (14.6)	3 (7.3)
Clinical benefit rate (CR + PR + SD-16 weeks[c])[e]		
n (%)	26 (63.4)	26 (63.4)
95% CI[b]	(46.9, 77.9)	(46.9, 77.9)
Disease control rate (CR + PR + SD)		
n (%)	32 (78.0)	31 (75.6)
95% CI[b]	(62.4, 89.4)	(59.7, 87.6)
Duration of response[f,g]		
Responders, n	18	18
Median in months (95% CI)	24.54 (9.2, NE)	18.43 (9.2, NE)
Censored, n (%)	11 (61.1)	9 (50.0)
Reason censored		
Alive without documented disease progression	9 (50.0)	7 (38.9)
Subsequent anticancer therapy or cancer-related surgery without documented PD	1 (5.6)	1 (5.6)
Died or documented PD after missing 2 or more consecutive visits	1 (5.6)	1 (5.6)
Rate (%) of duration of response[f,h]		
6 months (95% CI)	81.1 (51.9, 93.5)	81.9 (53.8, 93.8)
12 months (95% CI)	73.7 (43.9, 89.3)	60.1 (31.3, 80.0)
Duration of follow-up (months)[f]		
Median	14.88	14.88
25th, 75th percentile	14.5, 28.8	9.2, 22.9

Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; N = number of patients in the population; n = number of patients per category; NE = not evaluable; PD = progressive disease; PR = partial response; *RET* = REarranged during Transfection; SD = stable disease; SD16+ = stable disease lasting 16 or more weeks.

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

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

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

c SD16+ indicates SD lasting 16 or more weeks following initiation of selpercatinib until the criteria for disease progression was first met.

d Includes 2 patients with xanthogranuloma , which cannot be evaluated by IRC due to being skin only in presentation.

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

f Estimate based on Kaplan-Meier method.

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

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

Note: Censored patients are represented as a percentage of responders by IRC assessment (N=18) and Investigator assessment (N=18).

Data cutoff date: 24 September 2021.

Table 24. Objective Response Rate, Best Overall Response, Duration of Response, and Clinical Benefit Rate (DCO 13 January 2023)

Tissue-Agnostic Efficacy Population, N	IRC	INV
	52	
Objective Response Rate[a,b], n (%); [95% CI]	23 (44.2); [30.5, 58.7]	24 (46.2) (32.2,60.5)
Complete response	3 (5.8)	4 (7.7)
Partial response	20 (38.5)	19 (36.5)
Clinical Benefit Rate (CR + PR + SD16+[c])[d], n (%); [95% CI[b]]	35 (67.3) [52.9, 79.7]	36 (69.2) (54.9,81.3)
Duration of Response[e,f], n; [censored (%)]	23; [44.2]	23; [44.2]
Median in months (95% CI)	37.19 (13.3, NE)	18.60 (9.8, NE)
Rate at 6 months[g] (95% CI)	84.7 (59.5, 94.8)	85.9 (62.2, 95.2)
Rate at 12 months[g] (95% CI)	79 (53.1, 91.6)	69.0 (43.2, 84.9)
Median Duration of Follow-Up (months)[e] (25^{th}, 75^{th} Percentile)	28.55 (11.2, 40.9)	28.55 (11.2, 31.4)

Abbreviations: CI = confidence interval; CR = complete response; INV = investigator; IRC = independent review committee; n = number of participants per category; N = number of participants in the analysis population; NE = not estimable; ORR = objective response rate; PR = partial response; SD16+ = stable disease lasting 16 or more weeks.

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

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

c SD16+ indicates SD lasting 16 or more weeks following initiation of selpercatinib until the criteria for disease progression was first met.

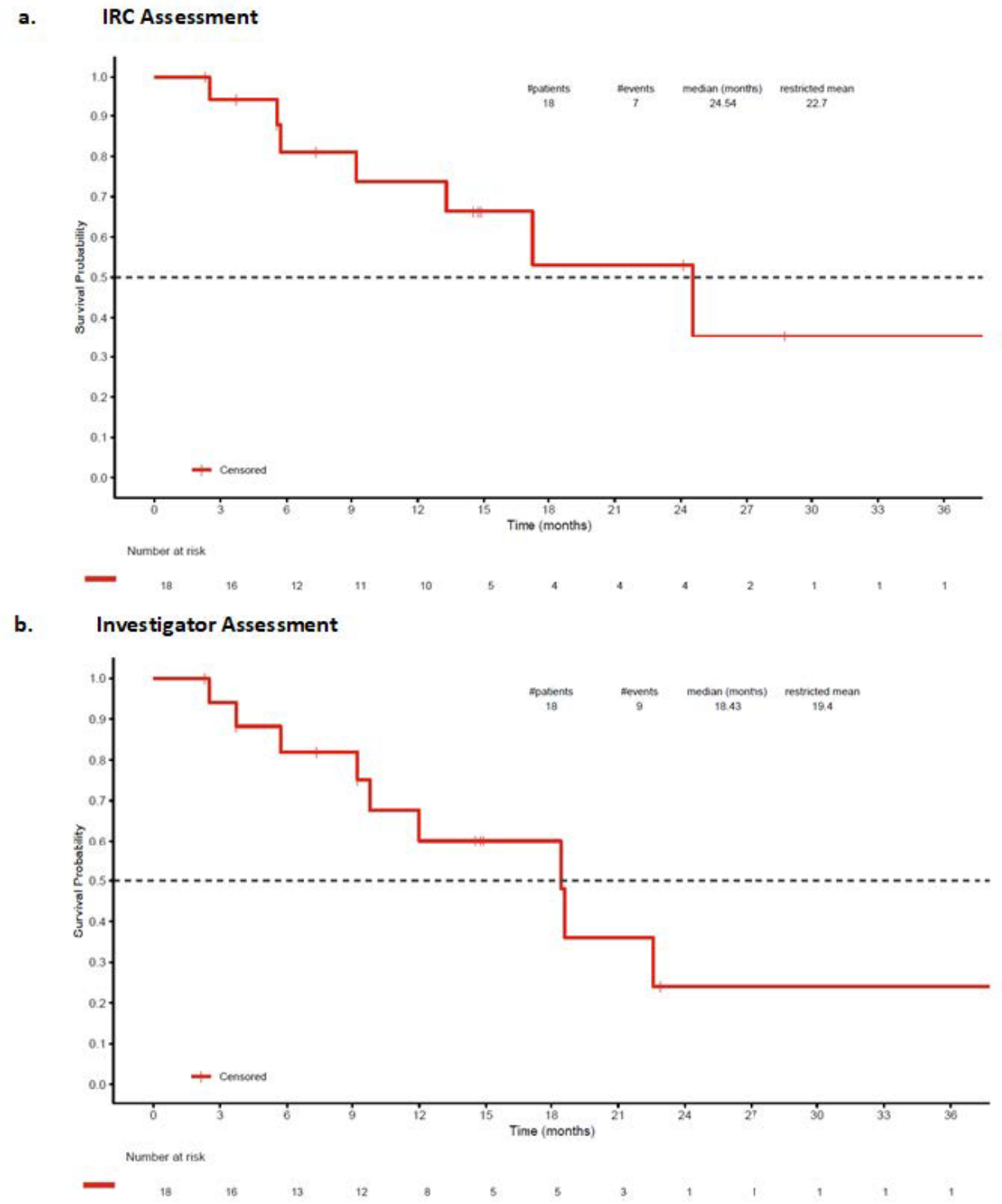
d Clinical benefit rate (%) is defined as the proportion of patients with best overall response of a confirmed CR, PR, or SD lasting 16 or more weeks (SD16+ weeks). SD was measured from the date of the first dose of selpercatinib until the criteria for disease progression or death was first met.

e Estimate based on the Kaplan-Meier method.

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

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

Figure 4. Kaplan-Meier plots for duration of response Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)



Abbreviation: IRC = Independent Review Committee.
Source: fdor_other_fusion_inv; fdor_other_fusion_irc

Sensitivity Analysis of Primary Endpoint of Objective Response Rate

Recommended Selpercatinib Dose

All but 1 patient received the RP2D of 160 mg BID.

- 40 patients (97.6%) received at least 1 dose of selpercatinib of 160 mg BID either:
    - as the starting dose (39 patients [95.1%]) or
    - through protocol-allowed intrapatient dose escalation (1 patient [2.4%]), and
- 1 patient (2.4%), enrolled in the Phase 1 dose escalation, received a starting dose of 120 mg BID and was never escalated to 160 mg BID

Measurable Disease

A sensitivity analysis for the primary endpoint of ORR and DOR based on IRC assessment was conducted for the 37 patients who:

- had at least 1 measurable lesion or
- had non measurable disease only and achieved a CR.

Table 25. Best Overall Response, Objective Response Rate, and Clinical Benefit Rate Based on IRC assessments – sensitivity analysis for patients with measurable or non measurable disease with BOR of CR (DCO 24 September 2021)

Status	RET Fusion Colon (N=10)	RET Futon Pancreas (N=11)	Total RET Fusion Non-Lung/Tyroid Solid Tumors (N=37)
Best Overall Response (n, %) [1]			
Complete Response (CR)	0	0	2 (5.4)
Partial Response (PR)	2 (20.0)	6 (54.5)	16 (43.2)
Stable Disease (SD)	7 (70.0)	2 (18.2)	13 (35.1)
SD*	5 (50.0)	1 (9.1)	7 (18.9)
Progressive Disease (PD)	1 (10.0)	2 (18.2)	3 (8.1)
Not Evaluable (NE)	0	1 (9.1)	3 (8.1)
Objective Response Rate (CR + PR) [2,5]			
Number of Patients (n, %)	2 (20.0)	6 (54.5)	18 (48.6)
95% Confidence Interval	(2.5, 55.6)	(23.4, 83.3)	(31.9, 65.6)
Clinical Benefit Rate (CR + PR + SD*) [3,5]			
Disease Control Rate (CR + PR + SD) [4,5]			
Number of Patients (n, %)	9 (90.0)	8 (72.7)	31 (83.8)
95% Confidence Interval	(55.5, 99.7)	(39.0, 94.0)	(68.0, 93.8)

Efficacy eligible subjects are defined as the subjects whose first dose date is on or before 2021-03-24.
Percentage is calculated using the number of patients in the column heading as the denominator.
Stable Disease includes NON-CR/NON-PD.
* Indicates SD lasting >= 16 weeks following initiation of LOXO-292 until the criteria for disease progression was first met.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Objective Response Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, or PR. Response was confirmed by a repeat assessment no less than 28 days.
[3] Clinical Benefit Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or stable disease lasting 16 or more weeks (SD*). Stable disease was measured from the date of first dose of LOXO-292 until the criteria for disease progression was first met.
[4] Disease Control Rate (%) is defined as the proportion of patients with best overall response of confirmed CR or PR, or SD.
[5] 95% Confidence Interval was calculated using Clopper-Pearson method.

Time to Response (TTR) and Time to Best Response (TBR)

Table 26. Time to Response and Time to Best Response Tissue-Agnostic Efficacy analysis Set (DCO 24 September 2021)

Status	*RET* Fusion-Positive Tissue-agnostic Solid Tumors N=41	
	IRC Assessment	Investigator Assessment
Time to response (months)[a]		
Median	1.87	1.87
25th, 75th percentiles	1.7, 2.0	1.7, 2.0
Minimum, maximum	1.6, 3.9	0.7, 7.3
Time to response, n (%)		
<2 months	14 (77.8)	14 (77.8)
≥2 to <4 months	4 (22.0)	2 (11.1)
≥4 months	0 (0.0)	2 (11.1)
Time to best response (months)		
Median	1.87	1.87
25th, 75th percentiles	1.8, 2.0	1.8, 3.5
Min, max	1.6, 7.4	1.6, 7.3
Time to best response, n (%)		
<2 months	13 (72.2)	13 (72.2)
≥2 to 4 months	4 (22.0)	3 (16.7)
≥4 months	1 (5.6)	2 (11.1)

Abbreviations: IRC = Independent Review Committee; max = maximum; min = minimum; N = number of patients; n = number of patients in the specific category; *RET* = REarranged during Transfection.
Efficacy eligible patients are defined as the patients whose first dose date is on or before 24 March 2021.

Table 27 Time to Response and Time to Best Response Based on IRC Assessments Tissue-Agnostic Efficacy-Eligible Population (DCO 13 January 2023)

Status	RET Fusion Colon (N=13)	RET Fusion Pancreas (N=13)	Total RET Fusion Non Lung/Thyroid (N=52)
Patients with Best Response of Confirmed CR or PR [1][2]	4	7	23
Time to Response (months) [3]			
Median	3.73	1.87	1.87
25th, 75th Percentiles	2.8, 8.7	1.7, 3.6	1.8, 3.6
Minimum, Maximum	1.9, 13.6	1.6, 3.7	1.6, 13.6
Time to Response (n, %)			
<2 months	1 (25.0)	5 (71.4)	15 (65.2)
>= 2 to 4 months	2 (50.0)	2 (28.6)	7 (30.4)
>= 4 to 6 months	0 (0.0)	0 (0.0)	0 (0.0)
>= 6 to 9 months	0 (0.0)	0 (0.0)	0 (0.0)
>= 9 months	1 (25.0)	0 (0.0)	1 (4.3)
Time to Best Response (months) [4]			
Median	3.73	1.97	1.97
25th, 75th Percentiles	2.8, 8.7	1.7, 3.7	1.8, 3.7
Minimum, Maximum	1.9, 13.6	1.6, 13.8	1.6, 13.8
Time to Best Response (n, %)			
<2 months	1 (25.0)	4 (57.1)	13 (56.5)
>= 2 to 4 months	2 (50.0)	2 (28.6)	7 (30.4)
>= 4 to 6 months	0 (0.0)	0 (0.0)	0 (0.0)
>= 6 to 9 months	0 (0.0)	0 (0.0)	1 (4.3)
>= 9 months	1 (25.0)	1 (14.3)	2 (8.7)

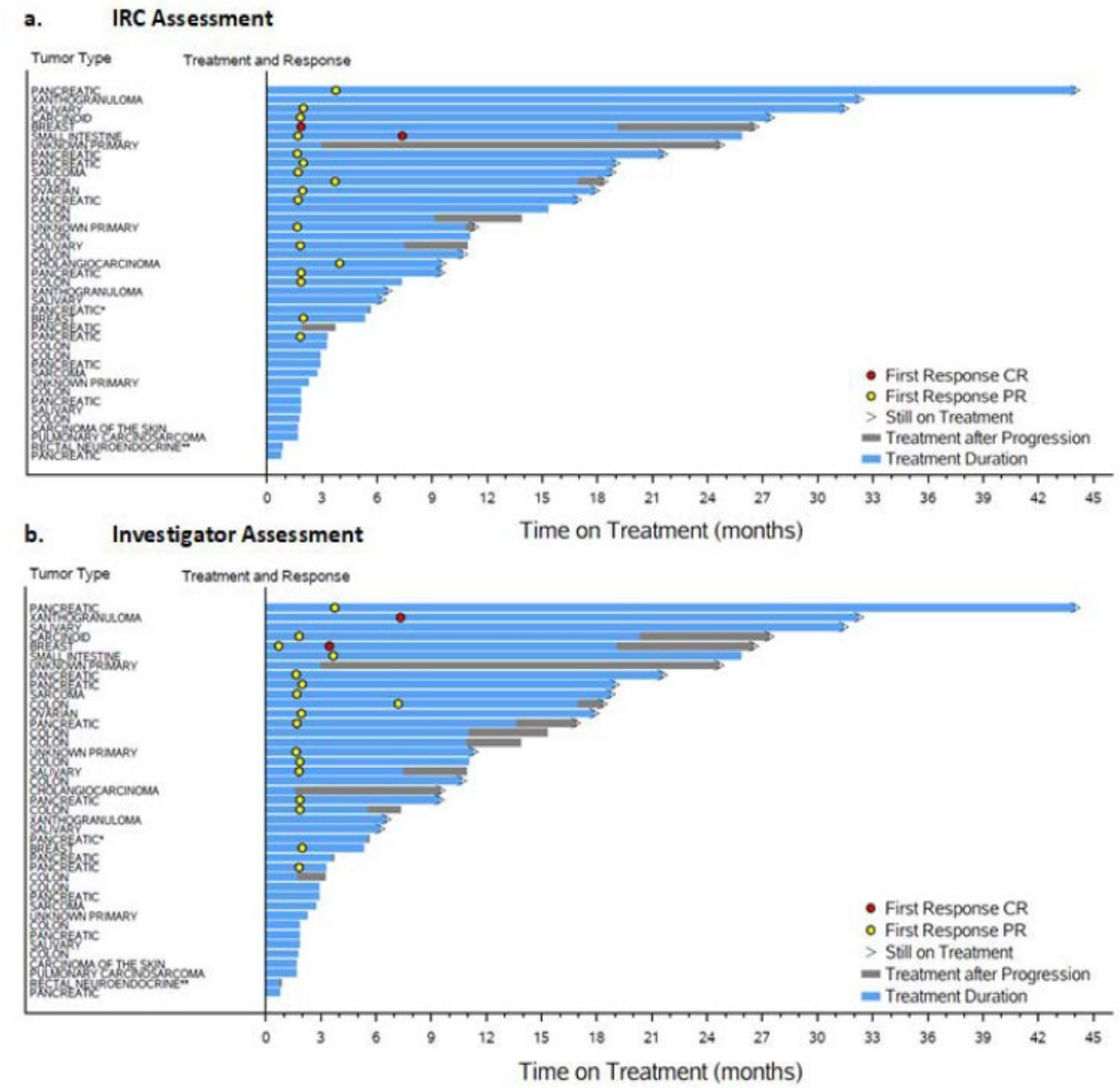
Efficacy eligible subjects are defined as the subjects whose first dose date is on or before 2022-07-13.
Percentage is calculated based on the number of patients with best response of confirmed CR or PR as denominator.
[1] Status as of the last contact on or before cutoff date.

[2] Based on IRC assessments using RECIST (version 1.1).
[3] Time to Response is defined as the number of months elapsed between the date of the first dose of LOXO-292 and the first documentation of objective response (CR or PR whichever occurred earlier) that was subsequently confirmed.
[4] Time to Best Response is defined as the number of months elapsed between the date of the first dose of LOXO-292 and the first documentation of CR (if patients best response is confirmed CR) or PR (if patients best response is confirmed PR) that was subsequently confirmed.

- Time on treatment relative to time to complete or partial response

Figure 5 shows individual time on treatment for all 41 patients in the Tissue-agnostic Efficacy Analysis Set, of which, 18 patients (43.9%) were still on treatment at the time of data cut-off. Patients who continued to benefit (as determined by the Investigator) from selpercatinib after disease progression were allowed to remain on treatment, per protocol, with Sponsor approval.

Figure 5. Swimmer plots of treatment duration with Complete Response or Partial Response Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)



Abbreviations: BID = twice daily; CR = complete response; IRC = Independent Review Committee; mon = months; PR = partial response.
*Starting dose 80 mg BID.
**Starting dose 120 mg BID.
Data cutoff date: 24 September 2021.
Sources: fswimmer_other_fusion_crpr_inv; fswimmer_other_fusion_crpr_irc

Progression-Free Survival

Median PFS by IRC was 13.24 months (95% CI: 7.4, 26.2), with a median follow-up of 16.43 months. Fourteen patients (34.1%) were progression free as of the 24 September 2021 data cut-off .

The progression-free rate at

- 12 months was 53.1%,
- 24 months was 32.1%, and
- 30 months was 24.1%.

The Kaplan-Meier plot of PFS by IRC is presented in Figure 4.

Observations based on Investigator assessments were in line with IRC assessments. The Kaplan- Meier plot of PFS by Investigator's assessments is presented in Figure 6.

Table 28. Progression-Free Survival Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)

	RET Fusion-Positive Tissue-agnostic Solid Tumors N=41	
Status	**IRC Assessment**	**Investigator Assessment**
Progression status, n (%)[a]		
Disease progression	11 (26.8)	19 (46.3)
Died (no disease progression beforehand)	9 (22.0)	5 (12.2)
Censored	21 (51.2)	17 (41.5)
Duration of progression-free survival (months)[b,c]		
Median	13.24	11.07
95% CI for median	7.4, 26.2	5.6, 19.1
Min, max	0.0+, 42.1+	0.0+, 42.1+
Duration of follow-up (months)[d]		
Median	16.43	16.56
25th, 75th percentiles	5.5, 30.2	9.0, 30.8
Rate (%) of progression-free survival[b,d]		
≥6 months (95% CI)	67.5 (48.8, 80.6)	58.1 (40.1, 72.4)
≥12 months (95% CI)	53.1 (34.1, 68.8)	43.1 (25.5, 59.6)
≥24 months (95% CI)	32.1 (14.0, 51.7)	22.4 (8.0, 41.2)
≥30 months (95% CI)	24.1 (7.7, 45.4)	16.8 (4.7, 35.4)

Abbreviations: + = censored observation; CI = confidence interval; INV = investigator; IRC = Independent Review Committee; N = number of patients; n = number of patients in the specific category; NE = not estimable; *RET* = REarranged during Transfection; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

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

[a] Based on INV assessments using RECIST 1.1.

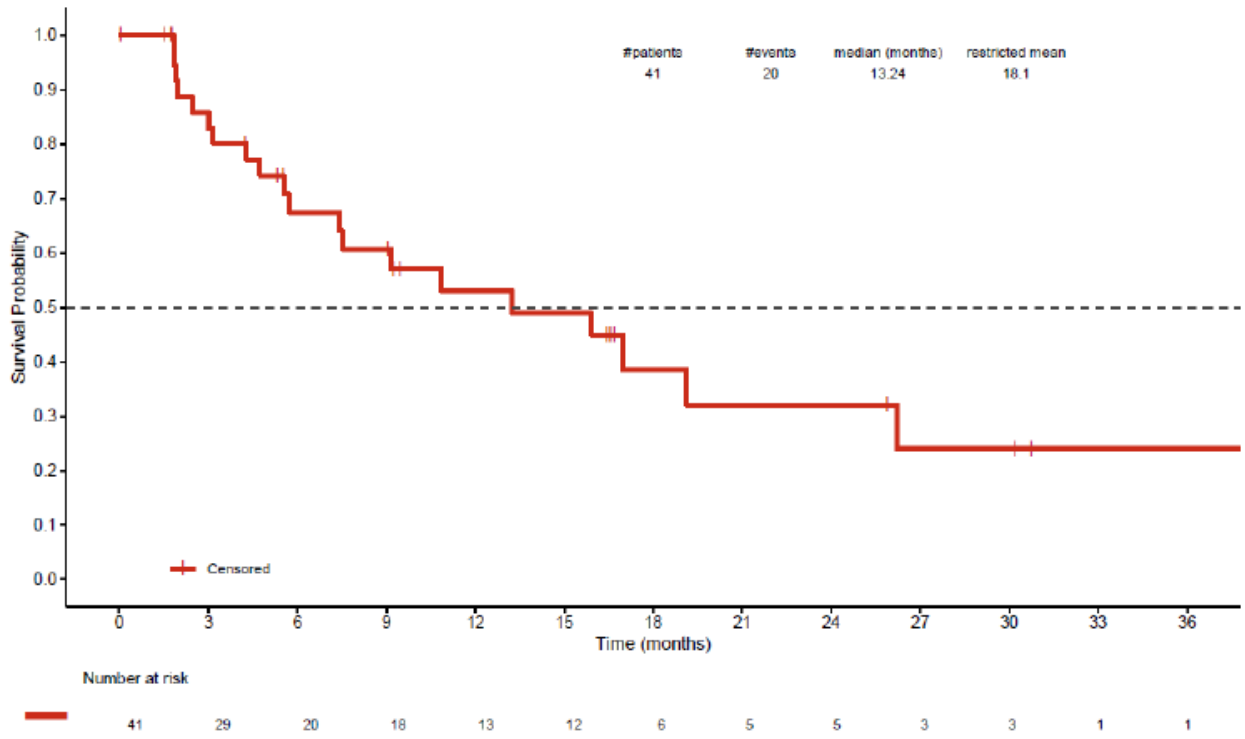
[b] Estimate based on Kaplan-Meier method.

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

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

Data cutoff: 24 September 2021.

Figure 6. Kaplan-Meier plot for Progression-Free Survival based on IRC Assessment Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)



Abbreviations: IRC = Independent Review Committee; RECIST = Response Evaluation Criteria in Solid Tumors.
Efficacy eligible patients are defined as the patients whose first dose date is on or before 24 March 2021.
Based on IRC assessments using RECIST 1.1.
Data cutoff date: 24 September 2021.

Table 29: Progression-Free Survival based on IRC assessments tissue-agnostic efficacy-eligible population (DCO13 January 2023)

Status	RET Fusion Colon (N= 13)	RET Fusion Pancreas (N= 13)	RET Fusion Non Lung/Thyroid (N= 52)
Status (n, %) [1]			
Disease Progression	5 (38.5)	5 (38.5)	17 (32.7)
Died (No Disease Progression Beforehand)	4 (30.8)	2 (15.4)	13 (25.0)
Censored	4 (30.8)	6 (46.2)	22 (42.3)
Reason Censored (n, %)			
Alive Without Documented Disease Progression	3 (23.1)	3 (23.1)	13 (25.0)
Died Or Documented Pd After Missing Two Or More Consecutive Visits	0 (0.0)	1 (7.7)	3 (5.8)
Discontinued From Study Without Documented Pd	0 (0.0)	0 (0.0)	3 (5.8)
Subsequent Anti-Cancer Therapy Or Cancer Related Surgery Without Documented Pd	1 (7.7)	2 (15.4)	3 (5.8)
Duration of Progression Free Survival (months) [2,3]			
Median	9.13	5.55	13.24
95% Confidence Interval for Median	4.0, 17.0	3.2, NE	5.6, 26.2
Minimum, Maximum	1.0, 24.8+	1.5+, 55.9	0.0+, 55.9
Duration of Follow-up (months) [4]			
Median	24.80	16.43	24.80
25th, 75th Percentiles	7.1, 24.8	11.0, 33.2	11.0, 33.2

Rate (%) of Progression Free Survival [2,3]			
6 months or more	67.1	48.6	61.3
95% Confidence Interval	34.2, 86.2	19.2, 73.0	45.7, 73.6
12 months or more	44.8	48.6	51.1
95% Confidence Interval	15.0, 71.1	19.2, 73.0	35.5, 64.7
18 months or more	11.2	48.6	42.7
95% Confidence Interval	0.6, 38.7	19.2, 73.0	27.4, 57.1
24 months or more	11.2	48.6	36.6
95% Confidence Interval	0.6, 38.7	19.2, 73.0	21.9, 51.4
30 months or more	NE	48.6	32.0
95% Confidence Interval	NE, NE	19.2, 73.0	17.3, 47.7

Efficacy eligible subjects are defined as the subjects whose first dose date is on or before 2022-07-13.
Percentage is calculated based on the number of patients in the column heading as the denominator.
[1] Based on IRC assessments using RECIST (version 1.1).
[2] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[3] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.
[4] Estimate based on Reverse Kaplan-Meier method. NE = Not estimable.

Overall Survival

Table 29 presents the OS in the Tissue-agnostic Efficacy Analysis Set. The median OS was 18.04 months (95% CI: 10.7, NE), with a median follow-up time of 18.76 months. The OS data are not yet considered mature, with a censoring rate of 56.1%. The Kaplan-Meier plot of OS is presented in Figure 7.

The rate of OS at:

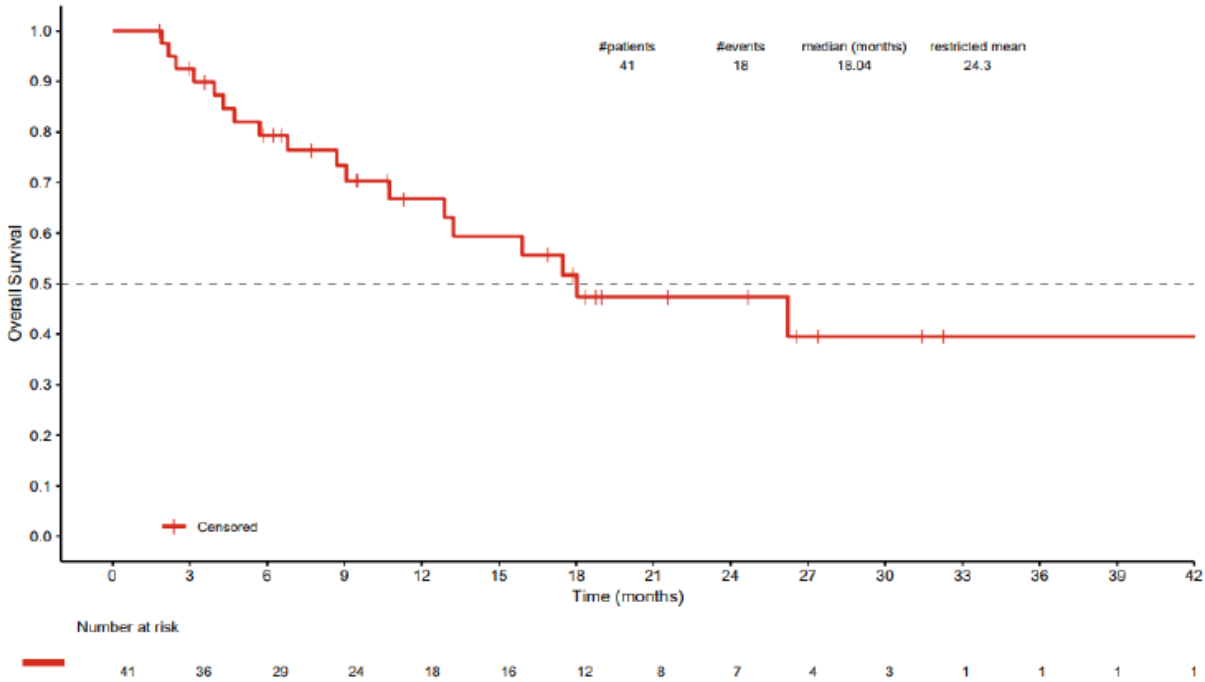
- 12 months was 66.8%,
- 24 months was 47.4%, and
- 30 months was 39.5%.

Table 30. Overall Survival Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)

Status	*RET* Fusion-Positive Tissue-agnostic Solid Tumors N=41
Survival status, n (%)	
Died	18 (43.9)
Censored	23 (56.1)
Duration of overall survival (months)[a,b]	
Median	18.04
95% CI for median	10.7, NE
Min, max	1.8+, 44.0 +
Duration of follow-up (months)[c]	
Median	18.76
25th, 75th percentiles	9.5, 26.5
Rate (%) of overall survival[a,b]	
≥12 months (95% CI)	66.8 (48.6, 79.8)
≥24 months (95% CI)	47.4 (28.7, 64.0)
≥30 months (95% CI)	39.5 (19.5, 59.0)

Abbreviations: + = censored observation; CI = confidence interval; max = maximum; min = minimum; N = number of patients in the specified category; NE = not estimable; *RET* = REarranged during Transfection.
Status as of the last contact on or before 24 September 2021.
Efficacy eligible patients are defined as the patients whose first dose date is on or before 24 March 2021.
[a] Estimate based on Kaplan-Meier method.
[b] 95% CI was calculated using Brookmeyer and Crowley method.
[c] Estimate based on Reverse Kaplan-Meier method.
Data cutoff: 24 September 2021.

Figure 7. Kaplan-Meier plot for overall survival Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)



Abbreviations: IRC = Independent Review Committee; RECIST = Response Evaluation Criteria in Solid Tumors.
Efficacy eligible patients are defined as the patients whose first dose date is on or before 24 March 2021.
Assessment made using RECIST 1.1.
Data cutoff date: 24 September 2021.

Table 31 Overall Survival Tissue-Agnostic Efficacy-Eligible Population (DCO 13 January 2023)

Status	RET Fusion Colon (N= 13)	RET Fusion Pancreas (N= 13)	RET Fusion Non Lung/Thyroid (N= 52)
Survival Status (n, %)			
Died	10 (76.9)	8 (61.5)	30 (57.7)
Censored	3 (23.1)	5 (38.5)	22 (42.3)
Reason Censored (n, %)			
Lost To Follow-Up	0 (0.0)	0 (0.0)	1 (1.9)
Os Follow Up Ongoing	3 (23.1)	5 (38.5)	19 (36.5)
Withdrawal Of Consent	0 (0.0)	0 (0.0)	2 (3.8)
Duration of Overall Survival (months) [1,2]			
Median	9.07	18.79	18.04
95% Confidence Interval for Median	6.8, NE	3.9, NE	10.7, 39.2
Minimum, Maximum	4.0, 30.7	2.2, 59.7+	1.4, 59.7+
Duration of Follow-up (months) [3]			
Median	26.32	34.63	33.22
25th, 75th Percentiles	26.3, NE	25.1, 37.2	19.4, 41.7
Rate (%) of Overall Survival [1,2]			
6 months or more	84.6	61.5	78.2
95% Confidence Interval	51.2, 95.9	30.8, 81.8	64.1, 87.3
12 months or more	48.1	53.8	63.0
95% Confidence Interval	18.4, 72.8	24.8, 76.0	47.7, 74.9
18 months or more	28.8	53.8	51.3
95% Confidence Interval	7.0, 55.9	24.8, 76.0	36.1, 64.6
24 months or more	19.2	44.9	44.0
95% Confidence Interval	3.0, 45.9	17.7, 69.0	29.2, 57.8
30 months or more	19.2	35.9	37.9
95% Confidence Interval	3.0, 45.9	11.7, 61.3	23.4, 52.3
36 months or more	NE	35.9	34.4
95% Confidence Interval	NE, NE	11.7, 61.3	20.2, 49.2

Efficacy eligible subjects are defined as the subjects whose first dose date is on or before 2022-07-13.
Percentage is calculated based on the number of patients in the column heading as the denominator.
[1] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[2] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.
[3] Estimate based on Reverse Kaplan-Meier method. NE = Not estimable.

Ancillary analyses

Exploratory Intrapatient Analyses

Intrapatient analysis was conducted in the 37 patients who had received systemic therapy prior to enrolment in LIBRETTO-001.

Objective response rate

The ORR for selpercatinib was higher than the ORR of 18.9% (n=7) for the last prior therapy.

Table 32. Best Response to Selpercatinib versus Immediate Prior Therapy Patients Who Received Prior Systemic Therapy Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)

	Patients Who Received Prior Systemic Therapy Tissue-agnostic Efficacy Analysis Set (N=37)
Patients responding to selpercatinib but not to prior therapy, n (%)	15 (40.5)
Patients responding to both selpercatinib and prior therapy, n (%)	2 (5.4)
Patients responding to prior therapy but not selpercatinib, n (%)	5 (13.5)
Patients who did not respond to selpercatinib or prior therapy, n (%)	15 (40.5)

Abbreviations: N = number of patients in the population; n = number of patients per category.

Table 33 Tumour Types for Patients Who Received Prior Systemic Therapy By Best Response to Selpercatinib versus Immediate Prior Therapy Tissue-Agnostic Efficacy-Eligible Population (DCO 13 January 2023)

Category	RET Fusion Agnostic (N= 52)
Patient responding to Selpercatinib but not prior therapy	19 (36.5)
Tumor Type (n, %)	
Pancreatic	6 (11.5)
Colon	5 (9.6)
Breast	2 (3.8)
Carcinoid	1 (1.9)
Carcinoma of the Skin	1 (1.9)
Ovarian	1 (1.9)
Salivary	1 (1.9)
Sarcoma	1 (1.9)
Unknown Primary	1 (1.9)
Number of Prior Lines of Therapy (n, %)	
1	5 (9.6)
2	8 (15.4)
3 or more	6 (11.5)
Patient responding to both Selpercatinib and prior therapy	2 (3.8)
Tumor Type (n, %)	
Pancreatic	1 (1.9)
Small Intestine	1 (1.9)
Number of Prior Lines of Therapy (n, %)	
1	1 (1.9)

Category	RET Fusion Agnostic (N= 52)
2	1 (1.9)
Patient responding to prior therapy but not Selpercatinib	6 (11.5)
Tumor Type (n, %)	
Pancreatic	2 (3.8)
Colon	1 (1.9)
Pulmonary Carcinosarcoma	1 (1.9)
Salivary	1 (1.9)
Small Cell Lung Cancer	1 (1.9)
Number of Prior Lines of Therapy (n, %)	
1	1 (1.9)
2	5 (9.6)
Patient did not respond to either Selpercatinib or prior therapy	20 (38.5)
Tumor Type (n, %)	
Colon	7 (13.5)
Pancreatic	4 (7.7)
Cholangiocarcinoma	2 (3.8)
Salivary	2 (3.8)
Sarcoma	2 (3.8)
Carcinoma of the Skin	1 (1.9)
Neuroendocrine	1 (1.9)
Rectal Neuroendocrine	1 (1.9)
Number of Prior Lines of Therapy (n, %)	
1	5 (9.6)
2	6 (11.5)
3 or more	9 (17.3)

Eligible patients are defined as patients treated on or before 13-JUL-2022.
Percentage is calculated using the number of patients in the column heading as the denominator.

Table 34. Response on Last Prior Systemic Therapy Compared to Selpercatinib Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)

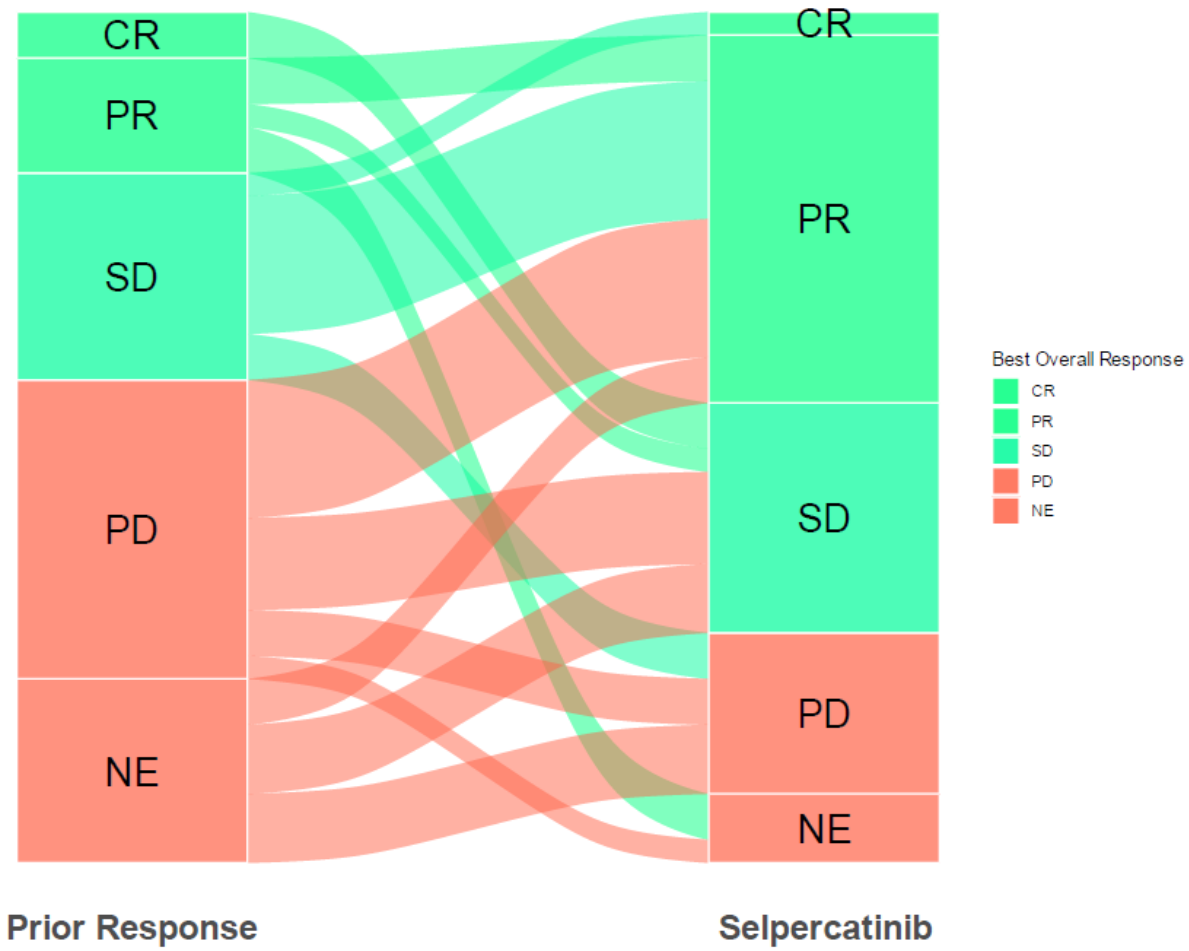
Patients with *RET* Fusion-Positive Tissue-agnostic Solid Tumors Who Received Prior Systemic Therapy N=37		
	Best Response to Last Systemic Therapy n (%)	**Best Response to Selpercatinib n (%)**
Responders	7 (18.9)	17 (45.9)
Complete response	2 (5.4)	1 (2.7)
Partial response	5 (13.5)	16 (43.2)
Nonresponders	30 (81.1)	20 (54.1)
Stable disease	9 (24.3)	10 (27.0)
Progressive disease	13 (35.1)	7 (18.9)
Not estimated	8 (21.6)	3 (8.1)

Abbreviations: N = number of patients; n = number of patients in the specific category; *RET* = REarranged during Transfection.

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

Note: McNemar exact test p-value = 0.253 assesses the significance of the difference between response rate for the last prior therapy versus response rate to treatment with selpercatinib.

Figure 8. Intrapatient flow and shift in response comparison between last prior treatment and treatment on selpercatinib Tissue-agnostic efficacy subset who received prior systemic therapy. (DCO 24 September 2021)

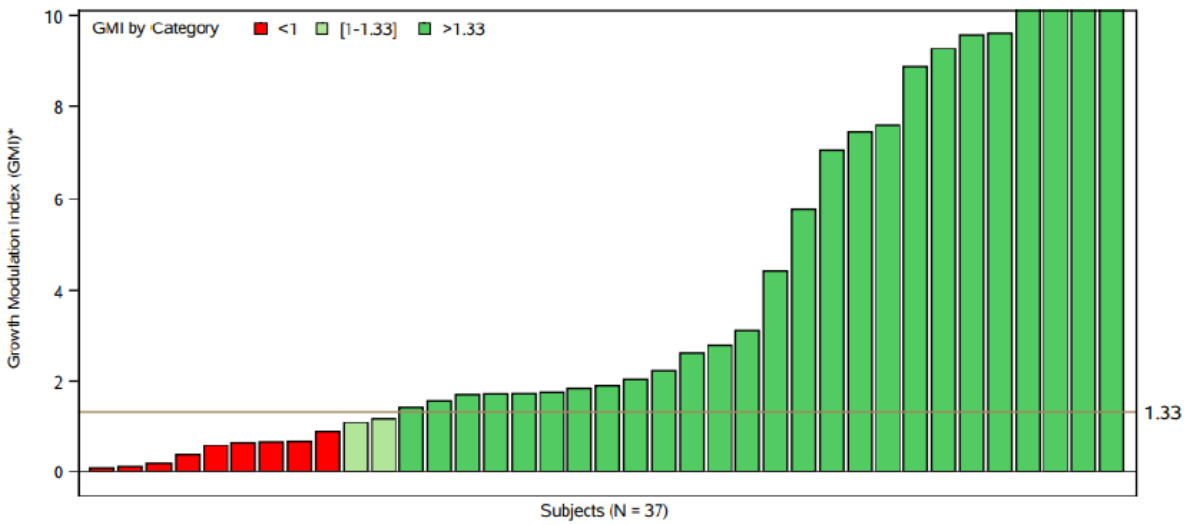


Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; NE = not evaluable.
Source: flpritrt_other_fusion_inv

Growth modulation index

Using time on treatment as a surrogate endpoint for the time patients are deriving clinical benefit from the treatment, a Growth Modulation Index (GMI) was calculated as the ratio of time on selpercatinib treatment to time on the last prior therapy (Figure 9). In the majority of patients (n=28 [75.7%]), the GMI was 1 or above, indicating that most patients stayed on treatment with selpercatinib, at minimum, as long as on the last prior therapy (derived benefit).

Figure 9. Waterfall plot of individual patient growth modulation indices. (DCO 24 September 2021)



Abbreviations: GMI = growth modulation index; N = number of patients.
Note: GMI ≥10 is displayed as 10.

Subgroup Analysis

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

Other subgroup analysis by demographics and baseline characteristics included age, sex, race,

ECOG performance status at baseline (0, 1 to 2), type of RET fusion gene, history of any metastatic diseases, number of prior systemic therapies (0, 1, 2, or 3 or more), prior immunotherapy (yes, no), and prior MKI (yes, no).

- Response by Demographic and Baseline Characteristics

Table 35. Objective Response Rate and Duration of Response in Subgroup Populations Based on IRC assessment Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)

	Patients (N)	*RET* Fusion-Positive Tissue-agnostic Solid Tumors			
		ORR		DOR (months)	
		n (%)	95% CI	Median	Range
All patients	41	18 (43.9)	(28.5, 60.3)	24.5	2.3+, 38.3+
Age at enrollment					
Less than 65 years	30	17 (56.7)	(37.4, 74.5)	17.3	2.3+, 38.3+
Greater than or equal to 65 years	11	1 (9.1)	(0.2, 41.3)	NR	28.8+
Sex					
Male	19	6 (31.6)	(12.6, 56.6)	24.5	5.7, 28.8+
Female	22	12 (54.5)	(32.2, 75.6)	17.3	2.3+, 38.3+
Race					
White	28	11 (39.3)	(21.5, 59.4)	24.5	2.3+, 38.3+
Asian	10	7 (70.0)	(34.8, 93.3)	17.3	5.6, 17.3
Other	3	0 (0.0)	(0.0, 70.8)	NE	NE
ECOG performance status at baseline					
0	14	6 (42.9)	(17.7, 71.1)	NR	3.7+, 14.9+
1	25	12 (48.0)	(27.8, 68.7)	24.5	2.3+, 38.3+
2	2	0 (0.0)	(0.0, 84.2)	NE	NE
***RET* fusion gene**					
KIF5B	4	1 (25.0)	(0.6, 80.6)	9.2	9.2
CCDC6	6	4 (66.7)	(22.3, 95.7)	NR	2.3+, 24.1+
Non-KIF5B/ non-CCDC6	31	13 (41.9)	(24.6, 60.9)	24.5	2.5, 38.3+
Metastatic disease					
Yes	39	18 (46.2)	(30.1, 62.8)	25.5	2.3+, 38.3+
No	2	0 (0.0)	(0.0, 84.2)	NE	NE
Number of prior systemic therapies					
0	4	0 (0.0)	(0.0, 60.2)	NE	NE
1	9	6 (66.7)	(29.9, 92.5)	NR	3.7+, 28.8+
2	15	7 (46.7)	(21.3, 73.4)	24.5	2.5, 38.3+
3 or more	13	5 (38.5)	(13.9, 68.4)	9.5	2.3+, 14.8+
Prior immunotherapy					
Yes	7	2 (28.6)	3.7, 71.0	NR	5.7 14.8+
No	34	16 (47.1)	29.8, 64.9	24.5	2.3+, 38.3+
Prior anti-PD-1/PD-L1 therapy					
Yes	7	2 (28.6)	(3.7, 71.0)	NR	5.7, 14.8+

No	34	16 (47.1)	(29.8, 64.9)	24.5	2.3+, 38.3+
Prior multikinase inhibitor					
Yes	4	0 (0.0)	(0.0, 60.2)	NE	NE
No	37	18 (48.6)	(31.9, 65.6)	24.5	2.3+, 38.3+
Type of RET molecular assay					
NGS on blood or plasma	3	0 (0.0)	(0.0, 70.8)	NE	NE
NGS on tumor	36	17 (47.2)	(30.4, 64.5)	24.5	2.3+, 38.3+
FISH	1	0 (0.0)	(0.0, 97.5)	NE	NE
Other[a]	1	1 (100.0)	(2.5, 100.0)	NR	5.56+

Abbreviations: + = censored observation; CI = confidence interval; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescent in situ hybridization; IRC = Independent Review Committee; N = number of patients; n = number of patients in the specific category; NE = not evaluable; NGS = next-generation sequencing; NR = not reached; ORR = objective response rate; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; RECIST = Response Evaluation Criteria in Solid Tumors; *RET* = REarranged during Transfection.

[a] Other molecular assay type is Liquid Biopsy using NGS.

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

Percentage is based on the number of patients (N) as the denominator.

Based on IRC assessments using RECIST 1.1.

Data cutoff date: 24 September 2021.

- Efficacy Results by Tumour Type and RET Fusion Partners

  Objective Response Rate and Duration of Response

Due to the rarity of tumour types with a low prevalence, a limited number of patients were enrolled in certain tumour type subgroups. Responses were seen in all tumour types evaluable by imaging with a sample size of 2 patients or more.

Overall IRC assessment determined that

- 18 patients across 10 of the 14 tissue-agnostic tumour types demonstrated a response
    - 16 patients had a PR (breast, carcinoid, cholangiocarcinoma, colon, ovarian, pancreatic, salivary, sarcoma, and unknown primary)
- clinical benefit was observed in 26 patients
- disease control was observed in 32 patients
- 28 of the evaluable 35 patients demonstrated a reduction in tumor size from baseline, and
- the median time to best response was 1.87 months.

Table 36. Objective Response Rate and Duration of Response Assessment by Tumour Type Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)

	N	% ORR (95% CI)	Median DOR in Months (Range)[a]	% CBR (95% CI)	% DCR (95% CI)
Tissue-Agnostic Efficacy Population	41	43.9 (28.47, 60.25)	24.54 (2.30+, 38.34+)	63.4 (46.94, 77.88)	78.0 (62.39, 89.44)
Pancreatic	11	54.5 (23.38, 83.25)	NR (2.50, 38.34+)	63.6 (30.79, 89.07)	72.7 (39.03, 93.98)
Colorectal	10	20.0 (2.52, 55.61)	9.43 (5.55, 13.31)	70.0 (34.75, 93.33)	90.0 (55.50, 99.75)
Salivary	4	50.0 (6.76, 93.24)	NR (5.72, 28.78+)	75.0 (19.41, 99.37)	100.0 (39.76, 100.00)
Unknown primary	3	33.3 (0.84, 90.57)	9.23	66.7 (9.43, 99.16)	100.0 (29.24, 100.00)
Breast	2	PR, CR	17.28 (2.30+, 17.28)	100.0 (15.81, 100.00)	100.0 (15.81, 100.00)
Sarcoma	2	PR, SD	14.88+	50.0 (1.26, 98.74)	100.0 (15.81, 100.00)
Xanthogranuloma	2	NE, NE	NA	0.0 (0.00, 84.19)	0.0 (0.00, 84.19)
Carcinoid	1	PR	24.11+	100.0 (2.50, 100.00)	100.0 (2.50, 100.00)
Ovarian	1	PR	14.52+	100.0 (2.50, 100.00)	100.0 (2.50, 100.00)
Small intestine	1	CR	24.54	100.0 (2.50, 100.00)	100.0 (2.50, 100.00)
Cholangiocarcinoma	1	PR	5.55+	100.0 (2.50, 100.00)	100.0 (2.50, 100.00)
Pulmonary carcinosarcoma	1	NE	NA	0.0 (0.00, 97.50)	0.0 (0.00, 97.50)
Rectal neuroendocrine	1	NE	NA	0.0 (0.00, 97.5)	0.0 (0.00, 97.50)
Carcinoma of the skin	1	NE	NA	0.0 (0.00, 97.50)	0.0 (0.00, 97.50)

Abbreviations: + = censored observation; CBR = clinical benefit rate; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; IRC = Independent Review Committee; N = number of participants per primary diagnosis; NA = not applicable; NE = not estimable; NR = not reached; ORR = objective response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; *RET* = REarranged during Transfection.

[a] Range is provided when more than 1 responder is present.

Efficacy-eligible patients are defined as the patients whose first dose date was on or before 24 March 2021.

Based on RECIST version 1.1.

Table 37. Objective Response Rate and Duration of Response Assessment by Tumour Type Tissue-agnostic Efficacy Analysis Set (DCO 13 January 2023)

	N		% ORR (95% CI)	Median DOR in Months (Range)[a]	% CBR (95% CI)	% DCR (95% CI)
	N as of September 2021	N as of January 2023				
Tissue-Agnostic Efficacy Population	41	52	44.2 (30.47, 58.67)	37.19 (1.84+, 52.14)	67.3 (52.89, 79.67)	78.8 (65.30, 88.94)
Pancreatic	11	13	53.8 (25.13, 80.78)	52.14 (2.50, 52.14)	69.2 (38.57, 90.91)	76.9 (46.19, 94.96)
Colorectal	10	13	30.8 (9.09, 61.43)	13.31 (1.84+, 13.31)	76.9 (46.19, 94.96)	84.6 (54.55, 98.08)
Salivary	4	4	50.0 (6.76, 93.24)	21.45 (5.72, 37.19)	75.0 (19.41, 99.37)	100.0 (39.76, 100.00)
Cholangiocarcinoma	1	3	33.3 (0.84, 90.57)	14.82	66.7 (9.43, 99.16)	66.7 (9.43, 99.16)
Unknown primary	3	3	33.3 (0.84, 90.57)	9.23	66.7 (9.43, 99.16)	100.0 (29.24, 100.00)
Sarcoma	2	3	33.3 0.84, 90.57	NR 31.44+	66.7 (9.43, 99.16)	100.0 (29.24, 100.00)
Breast	2	2	PR, CR 15.81, 100	17.28 (2.30+, 17.28)	100.0 (15.81, 100.00)	100.0 (15.81, 100.00)
Xanthogranuloma	2	2	NE[a] 0,84.19	NA	0.0 (0.00, 84.19)	0.0 (0.00, 84.19)
Carcinoma of the skin	1	2	NE and PR, 1.26, 98.74	NR 14.82+	50 (1.26, 98.74)	50 (1.26, 98.74)
Carcinoid	1	1	PR 2.50, 100	NR 40.94+	100.0 (2.50, 100.00)	100.0 (2.50, 100.00)
Ovarian	1	1	PR 2.50, 100	NR 28.55+	100.0 (2.50, 100.00)	100.0 (2.50, 100.00)
Small intestine	1	1	CR 2.50, 100	24.54 24.54	100.0 (2.50, 100.00)	100.0 (2.50, 100.00)
Pulmonary carcinosarcoma	1	1	NE 0,97.50	NA	0.0 (0.00, 97.50)	0.0 (0.00, 97.50)

	N		% ORR (95% CI)	Median DOR in Months (Range)[a]	% CBR (95% CI)	% DCR (95% CI)
	N as of September 2021	N as of January 2023				
Rectal neuroendocrine	1	1	NE 0,97.50	NA	0.0 (0.00, 97.5)	0.0 (0.00, 97.50)
Neuroendocrine	-	1	PR 2.50, 100	NR 3.84+	100.0 (2.50, 100.00)	100.0 (2.50, 100.00)
Small cell lung cancer	-	1	SD 0,97.50	NA	0 (0, 97.50)	100.0 (2.50, 100.00)

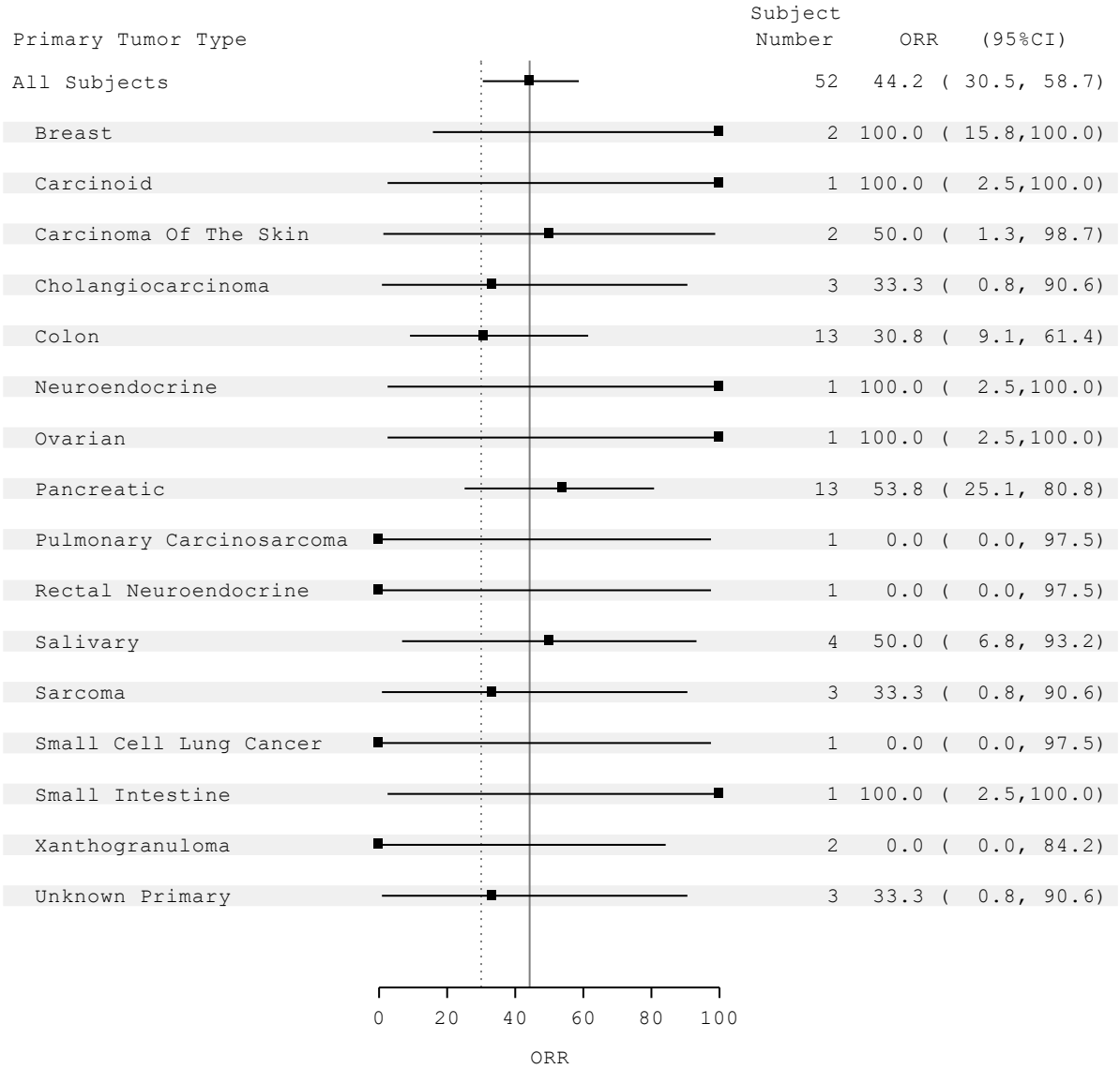
Abbreviations: + = censored observation; CBR = clinical benefit rate; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; IRC = independent review committee; N = number of participants per primary diagnosis; NA = not applicable; NE = not estimable; NR = not reached; ORR = objective response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease.

+ Denotes ongoing response.

[a] One patient with xanthogranuloma had disease that could not be evaluated by IRC due to skin being the only site of disease. Based on investigator assessment, this patient had a CR.

Efficacy-eligible patients are defined as the patients whose first dose date was on or before 13 January 2023.
Based on RECIST version 1.1.

Table 38 Forest plot of objective response rate in tumour type based on IRC assessments (DCO 13 January 2023)



Clinical benefit and disease control rate

Table 38 and Table 39 summarize the CBR and DCR by tumour type based on IRC and Investigator assessments.

Table 39. Summary of Clinical Benefit and Disease Control by Tumour Type Based on IRC Assessments Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)

		CBR			DCR		
	Patients (n)	No. of Patients with Clinical Benefit[1]	%	95% CI	No. of Patients with Disease Control[2]	%	95% CI
RET Fusion Positive Non	41	26	63.4	46.94, 77.88	32	78.0	62.39, 89.44
Lung/Thyroid Tumor Type							
Colon	10	7	70.0	34.75, 93.33	9	90.0	55.50, 99.75
Pancreatic	11	7	63.6	30.79, 89.07	8	72.7	39.03, 93.98
Carcinoid	1	1	100.0	2.50, 100.00	1	100.0	2.50, 100.00
Small Intestine	1	1	100.0	2.50, 100.00	1	100.0	2.50, 100.00
Salivary	4	3	75.0	19.41, 99.37	4	100.0	39.76, 100.00
Rectal Neuroendocrine	1	0	0.0	0.00, 97.50	0	0.0	0.00, 97.50
Xanthogranuloma	2	0	0.0	0.00, 84.19	0	0.0	0.00, 84.19
Breast	2	2	100.0	15.81, 100.00	2	100.0	15.81, 100.00
Ovarian	1	1	100.0	2.50, 100.00	1	100.0	2.50, 100.00
Sarcoma	2	1	50.0	1.26, 98.74	2	100.0	15.81, 100.00
Pulmonary Carcinosarcoma	1	0	0.0	0.00, 97.50	0	0.0	0.00, 97.50
Carcinoma Of The Skin	1	0	0.0	0.00, 97.50	0	0.0	0.00, 97.50
Cholangiocarcinoma	1	1	100.0	2.50, 100.00	1	100.0	2.50, 100.00
Unknown Primary	3	2	66.7	9.43, 99.16	3	100.0	29.24, 100.00

Cutoff Date: 2021-09-24.

Efficacy eligible subjects are defined as the subjects whose first dose date is on or before 2021-03-24.

Percentage is calculated based on the number of patients n as the denominator.

Based on IRC assessments using RECIST (version 1.1).

[1] Clinical Benefit is defined as the proportion of patients with best overall response of confirmed CR, PR, or stable disease lasting 16 or more weeks (SD*). Stable disease was measured from the date of first dose of LOXO-292 until the criteria for disease progression was first met.

[2] Disease Control is defined as the proportion of patients with best overall response of confirmed CR or PR, or SD.

95% Confidence Interval was calculated using Clopper-Pearson method.

Table 40. Summary of Clinical Benefit and Disease Control by Tumour Type Based on INV Assessments Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)

		CBR			DCR		
	Patients (n)	No. of Patients with Clinical Benefit[1]	%	95% CI	No. of Patients with Disease Control[2]	%	95% CI
RET Fusion Positive Non Lung/Thyroid Tumor Type	41	26	63.4	46.94, 77.88	31	75.6	59.70, 87.64
Colon	10	6	60.0	26.24, 87.84	7	70.0	34.75, 93.33
Pancreatic	11	7	63.6	30.79, 89.07	9	81.8	48.22, 97.72
Carcinoid	1	1	100.0	2.50, 100.00	1	100.0	2.50, 100.00
Small Intestine	1	1	100.0	2.50, 100.00	1	100.0	2.50, 100.00
Salivary	4	3	75.0	19.41, 99.37	3	75.0	19.41, 99.37
Rectal Neuroendocrine	1	0	0.0	0.00, 97.50	0	0.0	0.00, 97.50
Xanthogranuloma	2	2	100.0	15.81, 100.00	2	100.0	15.81, 100.00
Breast	2	2	100.0	15.81, 100.00	2	100.0	15.81, 100.00
Ovarian	1	1	100.0	2.50, 100.00	1	100.0	2.50, 100.00
Sarcoma	2	1	50.0	1.26, 98.74	2	100.0	15.81, 100.00
Pulmonary Carcinosarcoma	1	0	0.0	0.00, 97.50	0	0.0	0.00, 97.50
Carcinoma Of The Skin	1	0	0.0	0.00, 97.50	0	0.0	0.00, 97.50
Cholangiocarcinoma	1	0	0.0	0.00, 97.50	0	0.0	0.00, 97.50
Unknown Primary	3	2	66.7	9.43, 99.16	3	100.0	29.24, 100.00

Cutoff Date: 2021-09-24.

Efficacy eligible subjects are defined as the subjects whose first dose date is on or before 2021-03-24.

Percentage is calculated based on the number of patients n as the denominator.

Based on INV assessments using RECIST (version 1.1).

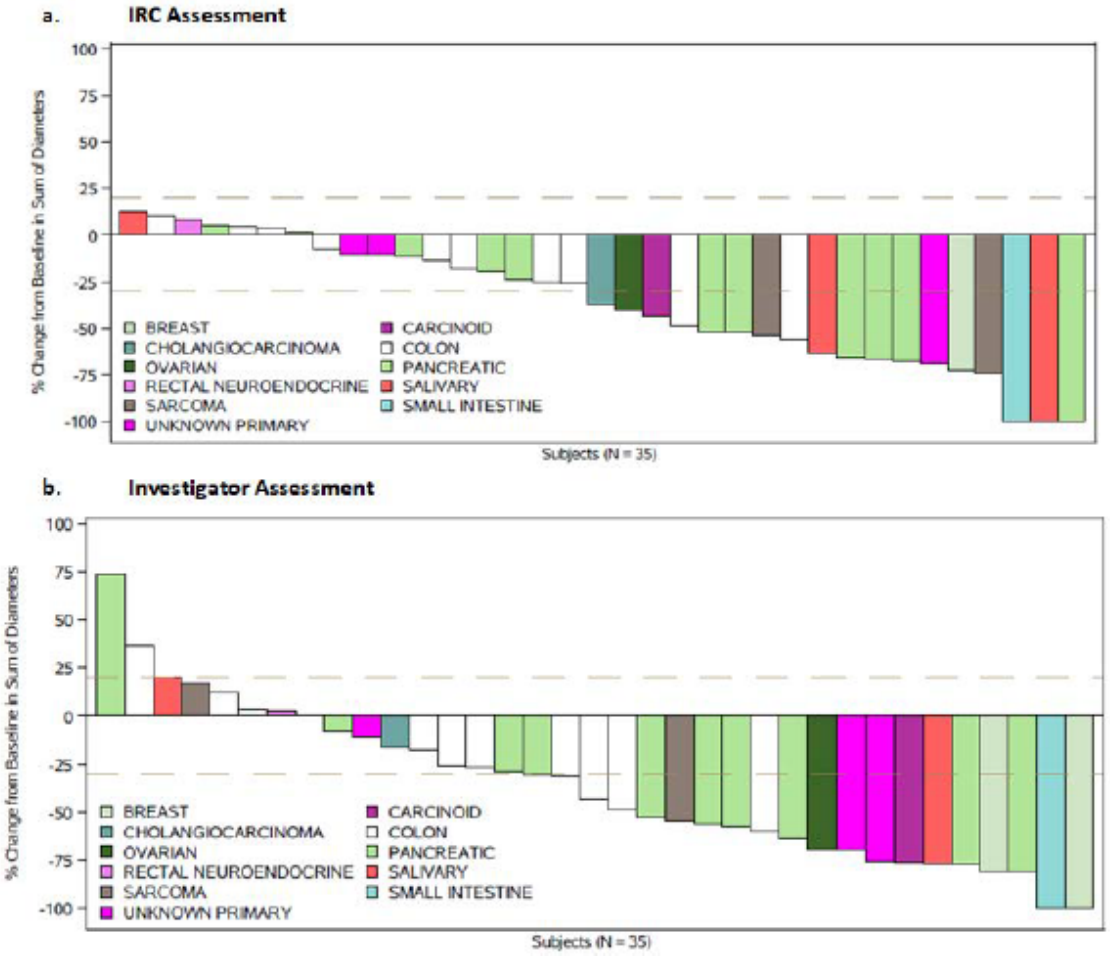
[1] Clinical Benefit is defined as the proportion of patients with best overall response of confirmed CR, PR, or stable disease lasting 16 or more weeks for patients with unconfirmed PR (uPR*) or Stable Disease (SD*). Stable disease was measured from the date of first dose of LOXO-292 until the criteria for disease progression was first met.

[2] Disease Control is defined as the proportion of patients with best overall response of confirmed CR or PR, or SD.

95% Confidence Interval was calculated using Clopper-Pearson method.

Best Change in Tumour Size by Tumour Type and RET Fusion Partner

Figure 10. Best change in tumour size by cancer type Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)



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

Notes: By IRC assessment, 6 patients had either nonmeasurable disease (5) or did not have postbaseline lesion measurements (1) and were therefore not included.

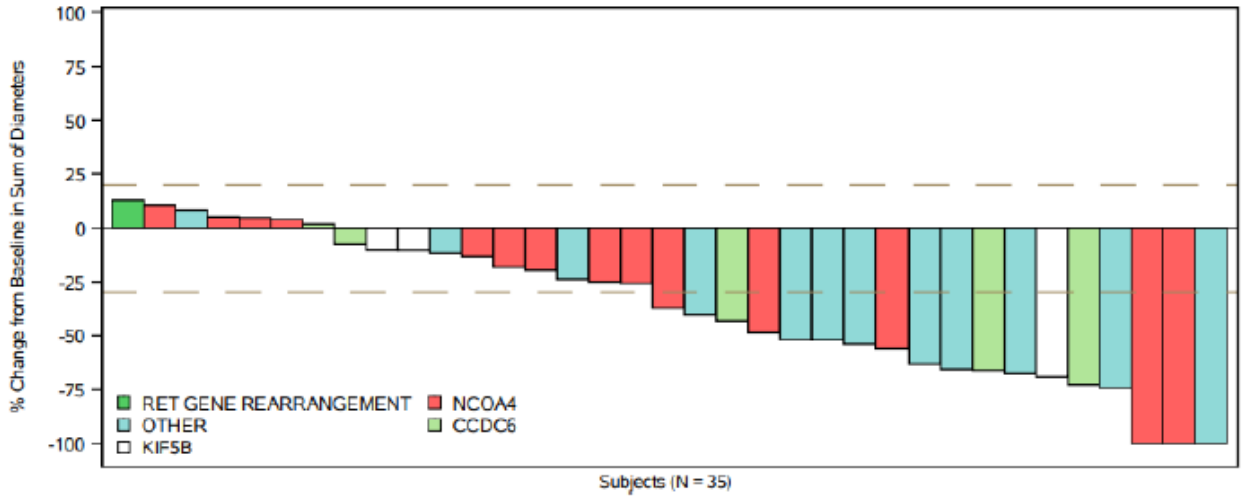
By Investigator assessment, 6 patients had either nonmeasurable disease (4) or did not have postbaseline lesion measurements (2) and were therefore not included.

For each patient, the best percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar.

Panel a: 2 patients (pancreatic and salivary cancer) who demonstrated 100% reduction in measurable lesions were determined to have a partial response, and 1 patient (small intestine cancer) with measurable disease was determined to have a complete response by IRC assessment. A patient with breast cancer had nonmeasurable disease only (not

included in Panel a) and was determined to have a complete response by IRC.
Panel b: 1 patient (small intestine cancer) who demonstrated 100% reduction in measurable lesions was determined to have a partial response, and 1 patient (breast cancer) with measurable disease was determined to have a complete response by Investigator assessment. A patient with xanthogranuloma had nonmeasurable disease only (not included in Panel b) and was determined to have a complete response by the Investigator.
Legend: The horizontal dashed lines represent the RECIST 1.1 threshold criteria for partial response (30% decrease) or progressive disease (20% increase).
Data cutoff date: 24 September 2021.

Figure 11. Best change in tumour size based on IRC assessments coloured by fusion partner Tissue-agnostic Efficacy Analysis Set (DCO 24 September 2021)



Abbreviations: IRC = Independent Review Committee; N = number of patients.
Efficacy eligible patients are defined as the patients whose first dose date is on or before 24 March 2021.
For each patient, the best percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar.
Note: Six patients are not included because they have nontarget lesion only or do not have postbaseline target lesion measurement based on IRC. Baseline is defined as the last available measurement prior to the first dose of selpercatinib.
Data cutoff date: 24 September 2021.
Source: fwaterfall_othfus_colorpart_irc

At 13 January 2023 DCO, 45 patients were eligible for change in tumour-size analysis. As determined by IRC assessment, 36 patients demonstrated a reduction in tumour size from baseline.

Analysis in most represented tumour types

Pancreatic cancer

As of the data cut-off date of 24 September 2021, 11 patients with *RET* fusion-positive pancreatic cancer were enrolled; all received at least 1 dose of selpercatinib of 160 mg BID as the starting dose (10 patients [91.0%]) or through protocol-allowed intrapatient dose escalation (1 patient [9.1%]).

Table 41. Overview of Patient Disposition in Patients with Pancreatic Cancer Tissue-Agnostic Efficacy Analysis Set (DCO 24 September 2021)

	RET Fusion-Positive Pancreatic Cancer N=11
Study Disposition	**n (%)**
Treatment status	
Discontinued	6 (54.5)
On treatment	5 (45.5)
Reason for treatment discontinuation	
Progressive disease	3 (27.3)
Adverse event	2 (18.2)
Withdrawal of consent	0 (0.0)
Death	1 (9.1)
Other	0 (0.0)
Lost to follow-up	0 (0.0)
Study status	
Discontinued	5 (45.5)
On study	6 (54.5)
Reason for study discontinuation	
Death	5 (45.5)
Withdrawal of consent	0 (0.0)
Lost to follow-up	0 (0.0)

Abbreviations: N = number of patients in the population; n = number of patients per category; *RET* = REarranged during Transfection.

Data cutoff date: 24 September 2021.

Source: Module 5, Tissue-Agnostic Interim CSR, Table 8.3

Table 42. Overview of Patient Demographics and Baseline Disease Characteristics and Prior Therapies in Patients with Pancreatic Cancer Tissue-Agnostic Efficacy Population (DCO 24 September 2021)

	***RET* Fusion-Positive Pancreatic Cancer** **N=11** **n (%)**
Demographics	
Sex	
Female	6 (54.5)
Male	5 (45.5)
Age	
Median years (min-max)	45 (31-65)
Overall age group	
18-44 years	5 (45.5)
45-64 years	5 (45.0)
65-74 years	1 (9.1)
75-84 years	0 (0.0)
≥85 years	0 (0.0)
Race	
White	9 (81.8)
Black or African American	0 (0.0)
Asian	2 (18.2)
Native Hawaiian or other Pacific Islander	0 (0.0)
Ethnicity	
Hispanic or Latino	0 (0.0)

	RET Fusion-Positive Pancreatic Cancer N=11 n (%)
Not Hispanic or Latino	11 (100.0)
Missing	0 (0.0)
ECOG performance status	
0	4 (36.4)
1	6 (54.5)
2	1 (9.1)
Baseline disease characteristics	
Fusion partner	11 (100.0)
NCOA4	2 (18.2)
CCDC6	2 (18.2)
KIF5B	0 (0.0)
RET gene rearrangement	0 (0.0)
Other[a]	7 (63.6)
Stage at entry	
Stage II	0 (0.0)
Stage III	0 (0.0)
Stage IV	11 (100.0)
Months since initial diagnosis	
Mean (SD)	14.25 (16.71)
Median	7.70
Min-max	4.1 – 61.5
History of metastatic disease	
Yes	11 (100.0)
No	0 (0.0)
Measurable disease (by Investigator assessment)	11 (100.0)
Measurable disease (by IRC assessment)	11 (100.0)
Prior cancer treatments	
Number of prior systemic regimens	
0	0 (0.0)
1	3 (27.3)
2	7 (63.6)
≥3	1 (9.1)
Median number of prior systemic regimens	2.0

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IRC = independent review committee; Max = maximum; Min = minimum; N = number of patients; n = number of patients in the specific category; *RET* = REarranged during Transfection; SD = standard deviation.
a Additional fusion partners: CGNL1 (n=1), ERC1 (n=1), GPHN (n=1), PRKAR1A (n=1), SPECC1L (n=1), TFG (n=1), and TRIM24 (n=1).
Data cut-off date: 24 September 2021

Of the 13 patients with pancreatic cancer at DCO 13 January 2023, 11 received fluoropyrimidine-based chemotherapy, one had only received cisplatin/gemcitabine, and one platins and etoposide. All 13 patients had at least 1 prior systemic therapy. The 2 patients who did not receive a fluoropyrimidine-containing regimen experienced PD as their BOR with selpercatinib

Table 43. Overview of Key Efficacy Results in Patients with Pancreatic Cancer Tissue-Agnostic Efficacy Population (DCO 24 September 2021)

	RET Fusion-Positive Pancreatic Cancer N=11	
	IRC Assessment	Investigator Assessment
Objective Response Rate[a,b]		
n (%)	6 (54.5)	6 (54.5)
95% CI	(23.4, 83.3)	(23.4, 83.3)
Best Overall Response, n (%)		
Complete response	0	0
Partial response	6 (54.5)	6 (54.5)
Stable disease	2 (18.2)	3 (27.3)
SD16+[c]	1 (9.1)	1 (9.1)
Progressive disease	2 (18.2)	1 (9.1)
Not evaluable	1 (9.1)	1 (9.1)
Clinical Benefit Rate (CR + PR + SD16+[c])[d]		
n (%)	7 (63.6)	7 (63.6)
95% CI[b]	(30.8, 89.1)	(30.8, 89.1)
Disease Control Rate (CR + PR + SD)		
n (%)	8 (72.7)	9 (81.8)
95% CI[b]	(39.0, 94.0)	(48.2, 97.7)
Duration of Response[e,f]		
Responders, n	6	6
Median in months (95% CI)	NE (2.5, NE)	NE (2.5, NE)
Range in months	2.5, 38.3+	2.5, 38.3+
Censored, n (%)	5 (83.3)	4 (66.7)
Reason Censored		
Alive without documented disease progression	4 (66.7)	3 (50.0)
Subsequent anticancer therapy or cancer-related surgery without PD	1 (16.7)	1 (16.7)
Died or documented PD after missing 2 or more consecutive visits	0 (0.0)	0 (0.0)
Remaining in Response[e,g]		
>at 6 months, % (95% CI)	83.3 (27.3, 97.5)	83.3 (27.3, 97.5)
>at 12 months, % (95% CI)	83.3 (27.3, 97.5)	55.6 (7.3 87.6)
Duration of Follow-Up (months)[e]		
Median	14.75	14.75

Abbreviations: + = censored observation; CI = confidence interval; CR = complete response; IRC = independent review committee; N = number of patients in the population; n = number of patients per category; NE = not evaluable; ORR = objective response rate; PR = partial response; *RET* = REarranged during Transfection; SD = stable disease; SD16+ = stable disease lasting 16 or more weeks.
a ORR is defined as the proportion of patients with best overall response of a confirmed CR or PR. Response was confirmed by a repeat assessment after 28 or more days.
b 95% CI was calculated using the Clopper-Pearson method.
c SD16+ indicates SD lasting 16 or more 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 a confirmed CR, PR, or SD lasting 16 or more weeks (SD16+ weeks). SD was measured from the date of the first dose of selpercatinib until the criteria for disease progression or death was first met.
e Estimate based on the Kaplan-Meier method.
f 95% CI was calculated using the Brookmeyer and Crowley method.
g 95% CI was calculated using the Greenwood's formula.
Note: Censored patients are represented as a percentage of responders by IRC assessment (N=6) and Investigator assessment (N=6).

- Intrapatient analysis of responses on selpercatinib versus prior therapy

Responses to selpercatinib were seen in 6 of the 11 patients with pancreatic cancer, all of whom received prior systemic therapy leading to an ORR of 54.5% based on Investigator assessment.

The ORR was 27.3% (3 of the 11 patients) for the last prior therapy. Of the 6 responders to selpercatinib treatment, 5 did not respond to the last prior therapy.

Median time on treatment with selpercatinib was 5.7 months (range: 0.8 to 44.0) and median time on the immediate prior treatment was 2.3 months (range: 0.8 to 26.5). In 8 patients (72.7%), GMI was above 1.33.

Colorectal Cancer

Table 44. Overview of Patient Disposition in Patients with Colorectal Cancer Tissue-Agnostic Efficacy Population (DCO 24 September 2021)

	***RET* Fusion-Positive Colorectal Cancer N=10**
Study Disposition	**n (%)**
Treatment status	
Discontinued	8 (80.0)
On treatment	2 (20.0)
Reason for treatment discontinuation	
Progressive disease	6 (60.0)
Adverse event	1 (10.0)
Withdrawal of consent	1 (10.0)
Death	0 (0.0)
Other	0 (0.0)
Lost to follow-up	0 (0.0)
Study status	
Discontinued	8 (80.0)
On study	2 (20.0)
Reason for study discontinuation	
Death	7 (70.0)
Withdrawal of consent	1 (10.0)
Lost to follow-up	0 (0.0)

Abbreviations: N = number of patients in the population; n = number of patients per category; *RET* = REarranged during Transfection.
Data cutoff date: 24 September 2021.
Source: Module 5, Tissue-Agnostic Interim CSR, Table 8.3

Table 45. Overview of Patient Demographics and Baseline Disease Characteristics and Prior Therapies in Patients with Colorectal Cancer Tissue-Agnostic Efficacy Population (DCO 24 September 2021)

	RET Fusion-Positive Colorectal Cancer N=10 n (%)
Demographics	
Sex	
Female	4 (40.0)
Male	6 (60.0)
Age	
Median years (min-max)	62 (32-85)
Overall age group	
18-44 years	1 (10.0)
45-64 years	4 (40.0)
65-74 years	3 (30.0)
75-84 years	1 (10.0)
≥85 years	1 (10.0)
Race	
White	6 (60.0)
Black or African American	1 (10.0)
Asian	2 (20.0)
Native Hawaiian or other Pacific Islander	1 (10.0)
Ethnicity	
Hispanic or Latino	1 (10.0)
Not Hispanic or Latino	9 (90.0)

Missing	0 (0.0)
ECOG performance status	
0	3 (30.0)
1	6 (60.0)
2	1 (10.0)
Baseline disease characteristics	
Fusion partner	10 (100.0)
NCOA4	9 (90.0)
CCDC6	1 (10.0)
KIF5B	0 (0.0)
RET gene rearrangement	0 (0.0)
Other	0 (0.0)
Stage at entry	
Stage II	1 (10.0)
Stage III	2 (20.0)
Stage IV	7 (70.0)
Months since initial diagnosis	
Mean (SD)	34.36 (24.0)
Median	31.15
Min-max	8.3 – 74.2
History of metastatic disease	
Yes	9 (90.0)
No	1 (10.0)
Measurable disease (by Investigator assessment)	10 (100)
Measurable disease (by IRC assessment)	10 (100)
Prior cancer treatments	
Number of prior therapies	
0	0 (0.0)
1	0 (0.0)
2	3 (30.0)
≥3	7 (70.0)
Median number of prior systemic regimens	3.5

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IRC = independent review committee; Max = maximum; Min = minimum; N = number of patients; n = number of patients in the specific category; *RET* = REarranged during Transfection; SD = standard deviation. Data cut-off date: 24 September 2021.

All 10 patients with colorectal cancer received FOLFOX, FOLFIRI, or CAPEOX, with or without bevacizumab, as recommended by National Comprehensive Cancer Network Guidelines, as first- or second-line therapy. Two of the 10 patients received 2 of these preferred regimens and 1 patient received all 3.

Genomic profile

NCOA4-RET fusion was the most common fusion partner found in patients with colorectal cancer, representing 90.0% of the population.

Two patients with colorectal cancer had genomic profiles that may have hampered their ability to respond to selpercatinib.

- One patient with a *KRAS A146V* alteration (potential codriving mutation) had a best response of PD.

- Another patient with a Microsatellite instability-high tumour had a response of SD lasting 16 weeks or more.

Other genomic alterations were detected as applicable by local laboratory testing; however, they were not deemed actionable in relation to colorectal cancer.

Table 46. Overview of Key Efficacy Results in Patients with Colorectal Cancer Tissue-Agnostic Efficacy Population (DCO 24 September 2021)

	RET Fusion-Positive Colorectal Cancer N=10	
	IRC Assessment	Investigator Assessment
Objective Response Rate[a,b]		
n (%)	2 (20.0)	3 (30.0)
95% CI	(2.5, 55.6)	(6.7, 65.2)
Best Overall Response, n (%)		
Complete response	0	0
Partial response	2 (20.0)	3 (30.0)
Stable disease	7 (70.0)	4 (40.0)
SD16+[c]	5 (50.0)	3 (30.0)
Progressive disease	1 (10.0)	3 (30.0)
Not evaluable	0	0
Clinical Benefit Rate (CR + PR + SD16+[c])[d]		
n (%)	7 (70.0)	6 (60.0)
95% CI[b]	(34.8, 93.3)	(26.2, 87.8)
Disease Control Rate (CR + PR + SD)		
n (%)	9 (90.0)	7 (70.0)
95% CI[b]	(55.5, 99.7)	(34.8, 93.3)
Duration of Response[e,f]		
Responders, n	2	3
Censored, n (%)	0	0
Median in months (95% CI)	9.43 (5.6, NE)	9.23 (3.7, NE)
Range in months	5.6, 13.3	3.7, 9.8
Remaining in Response[e,g]		
>at 6 months, % (95% CI)	50.0 (0.6, 91.0)	66.7 (5.4, 94.5)
>at 12 months, % (95% CI)	50.0 (0.6, 91.0)	0.0 (NE, NE)
Duration of Follow-Up (months)[e]		
Median	NE	NE

Abbreviations: CI = confidence interval; CR = complete response; IRC = independent review committee; N = number of patients in the population; n = number of patients per category; NE = not evaluable; ORR = objective response rate; PR = partial response; *RET* = REarranged during Transfection; SD = stable disease; SD16 = stable disease lasting 16 or more weeks.
a ORR is defined as the proportion of patients with best overall response of a confirmed CR or PR. Response was confirmed by a repeat assessment after 28 or more days.
b 95% CI was calculated using the Clopper-Pearson method.
c SD16+ indicates SD lasting 16 or more 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 a confirmed CR, PR, or SD lasting 16 or more weeks (SD16+ weeks). SD was measured from the date of the first dose of selpercatinib until the criteria for disease progression or death was first met.
e Estimate based on the Kaplan-Meier method.
f 95% CI was calculated using the Brookmeyer and Crowley method.
g 95% CI was calculated using the Greenwood's formula.
Note: Censored patients are represented as a percentage of responders by IRC assessment (N=2) and Investigator assessment (N=2).

- Intrapatient analysis of response on selpercatinib versus prior therapy

At 24 September 2021 data cut off, responses to selpercatinib were seen in 3 of the 10 patients who received prior systemic therapy leading to an ORR of 30.0% based on Investigator assessment. The ORR

was 10.0% (1 of the 10 patients) for the last prior therapy . Of the 3 responders to selpercatinib treatment, no one responded to the last prior therapy.

The median time on treatment with selpercatinib was 9.0 months (range: 1.8 to 18.3), and median time on the most recent prior treatment was 2.8 months (range: 1.0 to 7.5). In 7 (70%) patients, GMI was above 1.33.

Summary of main study

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

Table 47. Summary of Efficacy for Study LOXO-RET-17001 (Study J2G-OXJZJA; LIBRETTO-001)

Title: A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including *RET* Fusion-Positive Solid Tumors, Medullary Thyroid Cancer and Other Tumors with RET Activation (LIBRETTO-001)			
Study identifier	LOXO-RET-17001; (J2G-OX-JZJA ; LIBRETTO-001)		
Design	Phase 1/2, multicentre, open-label study that includes a Phase 1 dose escalation and a Phase 2 dose expansion component		
	Duration of main phase:		The study is ongoing. Patients are to be treated until there is evidence of progressive disease, unacceptable toxicity, or other reasons for treatment discontinuation as outlined in the protocol.
Hypothesis	Treatment of patients with advanced or metastatic *RET*-Fusion-Positive solid tumours with selpercatinib will provide a clinically meaningful increase in the ORR over standard of care, regardless of line of therapy.		
Treatments groups	Selpercatinib		Dose escalation: 20 mg once daily (QD) to 240 mg twice daily (BID). Phase 2: 160 mg BID
Endpoints and definitions	Primary endpoint	ORR, as assessed by the IRC	Estimated based on the proportion of patients with best overall response of confirmed CR or confirmed PR based on RECIST Version 1.1. Best overall response is defined as the best response designation for each patient that is recorded between the date of the first dose of selpercatinib and the date of documented disease progression per RECIST 1.1, as assessed by the IRC.
	Secondary endpoint	ORR, as assessed by the Investigator	Estimated based on the proportion of patients with best overall response of confirmed CR or confirmed PR based on RECIST Version 1.1. Best overall response is defined as the best response designation for each patient that is recorded between the date of the first dose of selpercatinib and the date of documented disease progression per RECIST 1.1, as assessed by the Investigator.
	Secondary endpoint	Duration of response by the IRC and the Investigator	The number of months from the start date of PR or CR, whichever response is recorded first, and subsequently confirmed, to the date of disease progression or death, whichever occurs earlier. Patients with time point responses, such as PR-NEPR or PR-Stable-PR, will be considered confirmed. For such patterns of response, the start date will be based on the date of the initial response.

	Secondary endpoint	Time to response by IRC and the Investigator	Number of months elapsed between the date of the first dose of selpercatinib and the first documentation of objective response (CR or PR, whichever occurs earlier) that is subsequently confirmed.
	Secondary endpoint	Time to best response by IRC and the Investigator	Number of months elapsed between the date of the first dose of selpercatinib and the first documentation of CR (if patient's best overall response is confirmed CR) or PR (if patient's best overall response is confirmed PR) that is subsequently confirmed.
	Secondary endpoint	Clinical benefit rate, as assessed by the IRC and the Investigator	The proportion of patients with best overall response of confirmed CR, PR, or SD, lasting 16 or more weeks following initiation of selpercatinib. SD will be measured from the date of the first dose of selpercatinib until the criteria for disease progression are first met.
	Secondary endpoint	Progression-free survival by the IRC and the Investigator	The number of months elapsed between the date of the first dose of selpercatinib and the earliest date of documented disease progression or death (whatever the cause).
	Secondary endpoint	Overall survival	The number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause). Patients who are alive or lost to follow-up as of the data cutoff date will be right-censored. The censoring date will be determined from the date the patient was last known to be alive.
Data cutoff date	13 January 2023		

Results and Analysis		
Analysis description	**Primary Analysis: Objective Response Rate by IRC**	
Analysis population and time point description	*RET* Fusion-Positive Tissue Agnostic (*RET*-Fusion-Positive solid tumours other than NSCLC or TC*)* Efficacy Population *Data cutoff date: 13 January 2023*	
Descriptive statistics and estimate variability	Treatment group	Selpercatinib
	Number of patients	N = 52
	Primary analysis: **Objective Response Rate[a,b] IRC Assessment** n (%) (95% CI)	 23 (44.2) (30.5, 58.7)
Analysis description	**Secondary Analysis: Objective Response Rate by Investigator**	
Analysis population and time point description	*RET* Fusion-Positive Tissue Agnostic Efficacy Population *Data cut-off date: 13 January 2023*	
	Treatment group	Selpercatinib
	Number of patients	N = 52

Descriptive statistics and estimate variability	Secondary analysis: **Objective Response Rate[a,b] Investigator Assessment** n (%) (95% CI)	24 (46.2%) (32.2, 60.5)	
Analysis description	**Other Secondary Analyses**		
Analysis population and time point description	*RET* Fusion-Positive Tissue Agnostic Efficacy Population *Data cutoff date: 13 January 2023*		
Descriptive statistics and estimate variability	Treatment group	Selpercatinib	
		IRC Assessment	**Investigator Assessment**
	Number of patients	N = 52	N = 52
	Number of responders	n = 23	n = 24
	Duration of Response (months)[c,d] Median (95% CI)	37.19 (13.3, NE)	18.6 (9.8, NE)
	Time to response (months)[e] Median (Minimum, Maximum)	1.87 (1.6, 13.6)	1.9 (0.7, 16.4)
	Time to Best Response (months)[f] Median (Minimum, Maximum)	1.97 (1.6, 13.8)	1.9 (1.6, 16.4)
	Clinical benefit rate (CR + PR + SD-16 weeks[g]) n (%) (95% CI)[b]	35 (67.3) (52.9, 79.7)	36 (69.2) (54.9, 81.3)
	Progression-free survival (months)[c,d] Median (95% CI)	13.2 (5.6, 26.2)	11.0 (5.4, 19.1)
	Rate of progression-free survival[c,h] at 6 months or more (95% CI) at 12 months or more (95% CI) at 18 months or more (95% CI) at 24 months or more (95% CI) at 30 months or more (95% CI)	61.3 (45.7, 73.6) 51.1 (35.5, 64.7) 42.7 (27.4, 57.1) 36.6 (21.9, 51.4) 32.0 (17.3, 47.7)	56.4 (41.2, 69.1) 46.5 (31.5, 60.1) 35.8 (21.7, 50.1) 30.0 (16.8, 44.4) 25.7 (12.8, 40.8)
	Duration of Overall Survival (months)[c,d] Median (95% CI)	18.0 (10.7, 39.2)	
	Rate of Overall Survival[c,h] at 12 months or more (95% CI) at 24 months or more (95% CI) at 30 months or more (95% CI)	63.0 (47.7, 74.9) 44.0 (29.2, 57.8) 37.9 (23.4, 52.3)	

Abbreviations: BID = twice daily; CI = confidence interval; CR = complete response; IRC = Independent Review Committee; N = total number of patients; n = number of patients in specific category; NE = not estimable; NSCLC = non-small cell lung cancer; ORR = objective response rate; PD = progressive disease PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; RET = REarranged during Transfection; SD = stable disease; TC = thyroid cancer.

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

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

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

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

[e] 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.

[f] 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.

[g] Clinical Benefit Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or stable disease lasting 16 or more weeks. The duration of stable disease was measured from the date of the first dose of selpercatinib until the criteria for disease progression was first met.

[h] 95% CI was calculated using Greenwood's formula. Note: Stable disease includes Non-CR/Non-PD for patients with non-measurable disease.

Note: Stable disease includes Non-CR/Non-PD for patients with non-measurable disease.

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

Not applicable.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study LIBRETTO-001 is an ongoing phase 1/2 Study assessing selpercatinib in patients with advanced solid tumours, including *RET* Fusion-Positive Solid Tumours. This is an open-label study, without comparator. Data for already approved indications of selpercatinib come from this same study.

The part I was a dose escalation phase in patients with advanced solid tumour with *RET* alterations/activation and the part II was a phase 2 part with 6 cohorts. Patients included in this submission could potentially be recruited in part I and part II, cohort 1 (advanced RET fusion+ solid tumour progressed or intolerant to standard first line therapy), cohort 2 (advanced RET fusion+ solid tumour without standard first line therapy) and cohort 5 (cohort 1-4, disease not measurable). Cohort 3 and 4 included patient with *RET* mutant MTC, cohort 6 required to have been previously treated by a RET inhibitor.

Main inclusion criteria for part I were patients with a locally advanced or metastatic solid tumour who have progressed on or are intolerant to standard therapy, or no standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or decline standard therapy.

Main inclusion criteria for part II required that patients failed or were intolerant to standard therapy (cohort 1, standard therapy were detailed for colorectal, pancreas and breast cancer) or patients could have received no prior standard-first line therapy if no standard therapy exists, or in the opinion of the

Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or decline standard therapy (cohort 2).

Patients with known primary driver alteration other than *RET*, clinically significant active cardiovascular disease or history of myocardial infarction, QTcF interval > 470 msec were excluded which is already specified in section 5.1 of the SmPC.

Patients from phase I and phase II were included in the efficacy analysis set. Patients from phase II were included in all available cohort the histology independent indication (except cohort 6 but this cohort require to have been previously treated by a RET inhibitor).

ORR based on IRC assessment using RECIST 1.1 was chosen as primary outcome with TTR, TTBR, DOR, PFS and OS as secondary endpoints. Given the design of the study (single arm), the inclusion of DoR, PFS and OS as secondary endpoints and the choice of the primary endpoint is acceptable.

Efficacy data and additional analyses

At the latest data cut-off (13 January 2023), 52 patients were included in the efficacy analysis set with *RET*-fusion positive tumour other than NSCLC and MTC were treated with selpercatinib. Of these, 16 patients (30.8%) were still on treatment at the data cut-off. Reasons for discontinuation were mainly disease progression (23 patients, 44.2%) and adverse events (5 patients, 9.6%).

Important protocol deviations were observed for 24.4% of patients. Among the protocol deviations reported, those who could have impacted the efficacy outcomes are for the majority (5/6) related to an incorrect dose reduction/holding and a drug compliance < 75%. Thus, more a negative impact on efficacy would be expected. Overall, the protocol deviations are unlikely to have impacted the claimed efficacy data.

Baseline data
In the tissue agnostic Efficacy-Eligible population, median age at baseline was 54.0 years with a wide range from 21 to 85 years. Each of the 18-44, 45-64 and 64-74 years category was represented with 30.8%, 40.4 and 21.2% respectively and with only 4 patients ≥75 years (including one patient ≥ 85 years). The sex ratio was around 1, most patients were white (67.3%) or Asian (25.0%) and ECOG at baseline was mainly 0 (30.8%) or 1 (61.5%).

In total, at the latest data cut-off (13 January 2023), 16 tumour types were represented, with the most common cancer being pancreas (13 patients) and colon (13 patients), followed by salivary (4 patients), unknown primary and sarcoma, cholangiocarcinoma (3 patients each) and breast, xanthogranuloma, and carcinoma of the skin (2 patients each). Ovarian, atypical carcinoid tumour, small intestine, pulmonary carcinosarcoma, neuroendocrine, small cell lung cancer and rectal neuroendocrine tumour were represented each by only one patient.

Information on other co-occurring mutations/alterations were provided. Of the 13 patients with colon cancer, 8 patients had MS-Stable, 3 MSI-H not detected and for one patient no information was available and one patient with MSI-H.

Co-occurring alterations were detected in 30 patients in the tissue-agnostic efficacy population, of whom one patient with colorectal cancer harboured a potential driver alteration (KRAS A146V).

Stage at diagnostic was mainly stage IV (84.4%) and median (min, max) months since initial diagnosis was 15.3 months (1.7, 213.2). 88.9% of patients had measurable disease by investigator assessment and 80% by IRC assessment. All patients had a RET fusion, with mainly NCOA4 (34.6%) and CCDC6 (17.3%) as fusion partner.

Most of the patients received a prior systemic therapy (90.4%, 37 patients) with a median of 2 prior systemic therapies (range 0 to 9) and 28.8% received 3 or more prior systemic therapies further data in most common type of cancer in the pivotal study (pancreas and colon) are provided below.

None of the patients had received prior treatment with a RET inhibitor, although according to the protocol, patients previously treated with a RET inhibitor were allowed to be enrolled in Cohort 6. This is reflected in section 5.1 of the SmPC.

At the DCO 13 January 2023, median time on treatment for the Tissue-Agnostic Safety Population was 7.6 months, thus limited. Median (range) relative dose-intensity was 97.8% (49.9-100.0) with 71.1% of patients who had a relative dose-intensity ≥ 90% and 15.6% of patients who had a relative dose intensity between 50 and <75%.

Outcomes

ORR was 43.9% by both IRC and INV assessment. Overall BOR were consistent between both assessments. Indeed, a low rate of CR (4.9%) was observed with mostly PR (39.0%) and SD (34.1%). Clinical benefit rate (CR+PR+SD ≥ 16 weeks) was evaluated at 63.4% and disease control rate (CR+PR+SD) at 78.0%.

Median duration of response (DoR) was 24.54 months according to IRC and although median DoR was lower according to investigator's assessment (18.43 months), these results, although a discrepancy is noticeable and probably related to the important impact of discrepancies between IRC and investigator's assessment in small sample size, suggest durable responses consistently with results in NSCLC and MTC indications.

A sensitivity analysis of ORR excluding one patient who never received 160 mg BID of selpercatinib showed consistent results (ORR 45%; 95% CI: 29.3, 61.5).

At the last DCO 13 January 2023, ORR by IRC was 44.2%, thus consistent with prior ORR of 43.9%. The rate of CR (5.8%), PR (38.5%) and CBR (67.3%) by IRC was also consistent with prior results. Overall, responses by INV were consistent with responses by IRC.

Median duration (95% CI) of response by IRC increased to 37.19 (13.3, NE) months compared to 24.54 (9.2, NE) months at prior DCO and rate of response at 6 months (84.7%) and at 12 months 78% also increased from prior DCO (81.1% and 73.7% respectively).

Median duration of follow-up was 28.55 months. Median time to response was 1.87 months corresponding to the first disease assessment.

Median PFS (95% CI) was 13.24 (5.6, 26.2) according to IRC consistently with previously submitted data. Median duration of follow-up was 24.80 months.

Median OS (95% CI) was 18.4 (10.7, 39.2) months with median follow-up of 33.22 months. Rate of OS was 63.0% at 12 months, 44.0% at 24 months and 34.4% at 30 months.

Note that the interpretation of PFS and OS is hampered by the single arm design of the study.

Ancillary analysis

Exploratory Intrapatient Analyses

The MAH has provided results of an exploratory intrapatient analyses to compare BOR from the last line of prior systemic therapy received (collected retrospectively) with the Investigator-assessed BOR for selpercatinib. 15 patients (40.5%) responded to selpercatinib but not to previous therapy. Of the 37 patients that had received prior systemic therapy, 7 (18.9%) responded to prior therapy and 17 (45.9%) to selpercatinib. There were two patients responding to prior therapy but not to selpercatinib and 15

patients not responding to prior therapy that responded to selpercatinib. A total of 15 (40.5%) patients did not respond to selpercatinib or prior therapy.

Shift in response between last prior treatment and treatment on selpercatinib shows that a large part of patients who did not respond to last prior treatment achieved partial response or stable disease. In addition, an important part of patients with stable disease on last prior therapy achieved partial or complete response.

Growth modulation index (GMI) indicates that 70.3% of patients stayed on selpercatinib treatment longer than under their previous treatment suggesting a higher benefit from selpercatinib than from prior therapy. The GMI was above 1.33, a threshold proposed as a marker of meaningful clinical activity of a new treatment (Von Hoff 1998).

Subgroup analysis

Results of the subgroup analysis by demographic and baseline disease characteristics are difficult to interpret due to the design of the study (single-arm) and the small sample size. Of note, no responders were observed with selpercatinib in the 4 patients who had not received prior systemic therapy (i.e. 2 patients with cancers of unknown primary origin and 2 patients with xanthogranuloma) and in the 4 patients that had received prior multikinase inhibitor, although numbers are low to draw any conclusion.

Regarding age, only 4/15 patients > 65 years achieved a response although more than a quarter of patients (15/52 evaluable patients) were > 65 years old. This is likely due to the higher proportion of patients with pancreas cancer in the group < 65 years (12 patients vs none in ≥ 65 years) which is the tumor type with the better ORR and by the fact that patients >65 years of age tend to have more comorbidities than younger patient which could impact efficacy outcomes.

- Efficacy Results by Tumour Type and *RET* Fusion Partners

Subgroups analysis shows that response rates were variable according to tumour type but, nonetheless, were observed in most of the tumour type represented. Response rate appears very interesting for previously treated pancreatic tumour (n=11) noting, nevertheless, wide CI (ORR of 54.4%, 95% CI: 23.38, 83.25), and although results were less remarkable for colon tumours (n=10), it should be noted that all patients received at least 2 prior treatment lines (ORR of 20%, 95% CI: 2.52, 55.61). Furthermore, in all tumour types represented by 2 to 4 patients, objective responses were observed. Finally, in half of the tumour types represented by only one patient, objective response responses were still observed.

Non-clinical data suggest that selpercatinib can be effective against multiple *RET* fusion-positive tumour types. This is supported by a strong biological rationale regarding the driver character of RET-fusion. In the single cohort of patients with RET fusion-positive solid tumours reported by Parimi et al. 2023, the majority of RET fusions are mutually exclusive with other primary driver alterations. This is a pattern shared by other bona fide cancer drivers, and positions RET fusions as an oncogenic driver of disease and an activating genomic event leading to oncogene addiction, regardless of the tissue type in which they arise. .The antitumour activity of selpercatinib was (only) evaluated *in vivo* in *RET* fusion positive NSCLC and CRC models. However, according to regulatory guidelines ICHS9, the product is expected to be effective in tumours containing the same mutation, there is no obligation to conduct studies to demonstrate the efficacy of selpercatinib in each tumor, for the same type of tumour.

Of note, a statement has been included in section 5.1 of the SmPC regarding the uncertainty in the ORR estimate per tumour type (i.e. "*Due to the rarity of RET fusion-positive cancer, patients were studied across multiple tumour types with a limited number of patients in some tumour types, causing uncertainty in the ORR estimate per tumour type*. *The ORR in the total population may not reflect the*

expected response in a specific tumour type"). In addition, a warning on efficacy across tumour type was included in section 4.4, in line with other medicinal products with histology independent indications.

Considering the limited sample size a definitive conclusion on efficacy across (all) tumour types is challenging. This can be considered an inherent limitation in the context of applications for histology independent indications. As outlined above, the contribution of the non-clinical data to support the clinical activity of selpercatinib in a broad histology-independent indication, particularly in tumour types where no/low response rate has been observed, can be questioned. However, efficacy data across the different DCO showed consistent results. Besides, despite the limitations of the current dataset, the fact that selpercatinib has shown activity across different *RET* fusion-positive tumours with durable responses in around 800 patients enrolled in the LIBRETTO-001 study is somehow reassuring in the context of the current procedure for a histology independent indication.

Analysis in most represented tumour types

Pancreatic cancer

At DCO 24 September 2021, the higher ORR of the efficacy analysis set was observed in patients with pancreatic cancer (53.8%, 6/11 patients). Objective responses were observed including in patients who did not respond to last prior therapy. At the DCO, 4 patients were still on treatment without PD. Median duration of response was not evaluable after a median follow-up of 14.75 months with 83.3% of patients whose response duration was > 12 months according to IRC (55.6% according to INV).

These observations suggest that selpercatinib could be of benefit in particular in patients with pancreatic cancer. This is also supported by GMI which shows a longer treatment duration on selpercatinib than on prior therapy for 72.7% of patients with pancreatic cancer.

At DCO January 2023, ORR by IRC was consistent at 53.8% (7/13 patients) with a median DoR of 52.14 months.

Colorectal Cancer

At DCO 24 September 2021 ORR was 20% in patients with colorectal cancer by IRC (30% by INV). However, clinical benefit (CR+PR+SD > 16 weeks) was observed for 70% of patients by IRC (60% by INV) and disease control (CR+PR+SD) in 90% of patients (70% by INV).

According to baseline data, all patients received were at least in 2 prior treatment lines, of which 70% received at least 3 prior treatment line. In addition, none of the 3 responders by investigator's assessment, responded to prior treatment line. Furthermore, 70% of patients remained longer of selpercatinib than in prior treatment.

At DCO January 2023, ORR by IRC was consistent at 30.8% (4/13 patients) with a median DoR of 13.31 months.

Companion diagnostic

The Applicant clarified that RET fusion was tested locally and that concordance bridging studies showed concordance of 90.1% between these local tests and F1CDx which is the test selected for the tissue-agnostic solid tumour indication.

Clinical data supporting a histology-independent indication

The 16 tumour types represented in the selpercatinib analysis are consistent with the natural expression of *RET* in the tissue as reported in the literature (Kato et al. 2017; Kohno et al. 2020), and thus where enrolment in a clinical trial can be feasible.

Supporting that the tissue of origin is not an important effect modifier, responses were observed in 12 of 16 tumour types included in LIBRETTO-001, in addition to the already authorised indication in RET fusion NSCLC and TC (4 histologies), for a total of 17 out of 21 histologies. In addition, 2 other tumour types with RET fusion showed responses to selpercatinib (infantile fibrosarcoma and lipofibromatosis). It is acknowledged that selpercatinib has shown activity across different RET fusion-positive tumours with durable responses, which is reassuring in the context of the (current) extension of indication site and histology independent.

In order to investigate resistance mechanisms and their potential difference across tumour histologies, the MAH is recommended to provide the final analysis of ctDNA samples where available, from patients with RET-fusion positive solid tumours other than NSCLC and thyroid cancer in LIBRETTO-001 (REC).

The claimed indication can only be supported for patients who had exhausted all treatment options or for whom no optimal treatment option exists. Thus, the wording of the indication was modified accordingly.

Additional efficacy data needed in the context of a conditional MA

Considering the single arm design of the trial hampering assessment of time to event endpoints, and the limited size of the efficacy analysis set, the data cannot be considered comprehensive at the time of approval.

In order to provide a comprehensive data package and fulfil the CMA criteria, the MAH will submit as specific obligations (SOBs) an updated Tissue-agnostic Efficacy Analysis Set from the pivotal study LIBRETTO-001, with approximately 74 patients, and the results from the two randomized phase 3 trials J2G-MC-JZJC (LIBRETTO-431) comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC, and J2G-MC-JZJB (LIBRETTO-531) comparing selpercatinib to physician’s choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naive, RET-mutant MTC.

In addition, to further support the histology independent indication, the MAH will conduct an observational study collecting real-world data from at least 20 to 30 patients with RET fusion-positive tumours other than NSCLC, MTC, or TC (REC).

2.4.3. Conclusions on the clinical efficacy

Although limitations related to the design of LIBRETTO-001 study and the small efficacy data set do not allow to assess comprehensive data, the provided results in several tumour types other than NSCLC and MTC suggest that RETSEVMO is potentially beneficial across other tumour types. At last DCO, (i.e. 13 January 2023), selpercatinib has showed an ORR per IRC of 44.2% (95% CI: 30.5, 58.7) with a median DoR of 37.19 months (95% CI: 13.3, NE) in patients with RET-fusion positive solid tumours other than NSCLC and TC.

Those beneficial effects were observed in patients who have exhausted all available therapeutic options or for whom there is no recommended standard treatment. Consistently with the treated population and with regards to the limitations of the provided data, the claimed indication can only be supported for patients who had exhausted all treatment options or for whom no optimal treatment option exists. The wording of the indication was modified accordingly.

Considering the low level of evidence in the majority of the indications targeted, the MAH was invited to further justify the applied site and histology independent indication. Additional data and justifications

were provided taking into account the totality of tumor types in which an activity has been observed (>20), in addition to the already known efficacy in RET-fusion NSCLC and TC.

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

- In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive solid tumours other than NSCLC and thyroid cancer, the MAH should submit the final data from patients with RET-fusion positive solid tumours other than NSCLC and thyroid cancer enrolled in the pivotal study LIBRETTO-001. The CSR should be submitted by 31 December 2025
- In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive non-small cell lung cancer, the MAH should submit the clinical study report of the Phase 3 study J2G-MC-JZJC (LIBRETTO-431) comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC. The CSR should be submitted by 31 December 2024
- In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET-mutant medullary thyroid carcinoma, the MAH should submit the clinical study report of the Phase 3 study J2G-MC-JZJB (LIBRETTO-531) comparing selpercatinib to physician's choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naive, RET-mutant MTC. The CSR should be submitted by 30 September 2025

2.5. Clinical safety

Introduction

The results henceforth represent safety analyses with the data cut off of 24 September 2021 for the Tissue-Agnostic Safety Population and 15 June 2021 for the Overall Safety Population.

An updated safety data set with a total of 837 patients was submitted and assessed in the context of the annual renewal of Retsevmo (EMEA/H/C/005375/R/0026).

Safety data are available from a total of 806 patients in the LIBRETTO 001 study which is still ongoing. Of these, 45 (~ 6%) had *RET* fusion-positive tumour Agnostic (TA) including 21 (~ 47%) with pancreatic/colorectal tumours. In total, 14 unique tumour types are represented in the Tissue-Agnostic Safety Population. In the above population 4 (~9%) patients were not previously treated with systemic therapy.

Table 48. Safety Analysis Populations

Safety Analysis Population	Data Cutoff Date	Number of Treated Patients
Overall Safety Population	15 June 2021	796, including 43 patients with tissue-agnostic solid tumours[a]
Tissue-Agnostic Safety Population[a]	24 September 2021	45

[a] The 43 patients with tissue-agnostic solid tumours, who were included in the **Overall Safety Population** as of the 15 June 2021 data cutoff date, were included in the **Tissue-Agnostic Safety Population** as of the 24 September 2021 data cutoff date, along with 2 patients who were additionally enrolled between 15 June 2021 and 24 September 2021.

Patient exposure

Exposure

Through 24 September 2021, a total of 806 patients have been treated with selpercatinib at doses ranging from 20 mg QD to 240 mg BID, regardless of tumour type; most patients (96%) received at least 1 dose of the selpercatinib recommended dose (Phase 2 dose) of 160 mg BID.

In the tumour agnostic safety population 21 patients were still receiving selpercatinib and 5 patients were in follow-up, but off treatment.

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

The most common reason for treatment discontinuation in the Tumour Agnostic Safety Population was disease progression (28.9%), followed by AE (8.9%).

In the tissue agnostic solid tumours Safety Population, 97.8% patients received at least 1 dose of selpercatinib 160 mg BID and 95.6% patients had a selpercatinib starting dose of 160 mg.

Table 49. Treatment and Study Disposition (*RET* Fusion Tumour Agnostic Safety population)

Status	RET Fusion Agnostic (N= 45)
Treatment Status (n, %)	
Discontinued	24 (53.3)
Continuing	21 (46.7)
Reason Treatment Discontinued (n, %)	
Progressive Disease	13 (28.9)
Adverse Event	4 (8.9)
Withdrawal of Consent	2 (4.4)
Lost to Follow-Up	1 (2.2)
Death	2 (4.4)
Other	2 (4.4)
Study Status (n, %)	
Discontinued	22 (48.9)
Continuing	23 (51.1)
Reason Study Discontinued (n, %)	
Withdrawal of Consent	2 (4.4)
Lost to Follow-Up	1 (2.2)
Death	19 (42.2)

The median time on treatment was 21.3 and 6.57 months, respectively, for the Overall Safety Population, and naïve overall Tumor Agnostic population.

The most reported dose modification was dose withheld (72.9% in the Overall Safety Population and 62.2% in the Tumor Agnostic Safety Population) primarily attributed to adverse events (AEs) (64.1% in the Overall Safety Population and 55.6% in the overall TA Safety Population).

Demographics and other baseline characteristics

As of 24 September 2021, the median age across the Tissue-agnostic Safety Analysis Set (N=45) was 53 years (range: 21 to 85 years); 51.1% of patients were female; 68% were Caucasian and 25% were Asian.

Exposure

Table 50. Selpercatinib Dose Intensity Tissue-agnostic Safety Analysis Set

	***RET* Fusion-Positive Tissue-agnostic Solid Tumors (N=45)**
Time on treatment (months)[a]	
Median	6.6
Minimum	0.6
Maximum	44.0
Relative dose intensity[b] (%)	
Mean (standard deviation)	90.1 (13.8)
Median	97.8
Range	49.9-100.0
Relative dose intensity category, n (%)	
≥90%	32 (71.1)
75-<90%	5 (11.1)
50-<75%	7 (15.6)
<50%	1 (2.2)

Abbreviations: N = number of patients in the safety population; n = number of patients per category; *RET* = REarranged during Transfection.
Percentage is calculated based on the number of patients in the column heading as the denominator.
[a] Time on Treatment (TOT) (months) = (last dose date - first dose date + 1)/30.4375 for patients who discontinued selpercatinib as of the data cutoff date; TOT (months) = (data cutoff date - first dose date + 1)/30.4375 for subjects continuing to receive selpercatinib as of the data cutoff date.
[b] Relative dose intensity (%) = (actual dose intensity [ADI]/planned dose intensity [PDI])×100.
Data cutoff date: 24 September 2021.

Dose modification

All but 1 patient in the Tissue-agnostic Safety Analysis Set received the RP2D of 160 mg BID:

- 44 patients (97.8%) received at least 1 dose of selpercatinib 160 mg BID either
    - as the starting dose (43 patients [95.6%]) or
    - through protocol-allowed intrapatient dose escalation (1 patient [2.2%])
- 1 patient (2.2%), enrolled in the Phase 1 dose escalation, received a starting dose of 120 mg BID, and was never escalated to 160 mg BID.
- 62.2% of patients had 1 or more doses withheld
- 55.6% of patients had 1 or more doses withheld due to a TEAE, and
- 28.9% of patients had at least 1 dose reduction due to a TEAE.

Table 51. Selpercatinib Dose Modifications Tissue-agnostic Safety Analysis Set

	RET Fusion-Positive Tissue-agnostic Solid Tumors (N=45) n (%)
Dose reduction	
Any	13 (28.9)
Due to an AE[a]	13 (28.9)
Due to other reasons	1 (2.2)
Dose withheld	
Any	28 (62.2)
Due to an AE[b]	25 (55.6)
Due to other reasons	9 (20.0)
Dose increase	
Any	7 (15.6)
Intrapatient escalation[c]	1 (2.2)
Dose re-escalation[d]	4 (8.9)
Other reasons	3 (6.7)

Abbreviations: AE = adverse event; N = number of patients in the safety population; n = number of patients per category; *RET* = REarranged during Transfection; TEAE = treatment-emergent adverse event.

[a] Patient 820-006 had TEAEs with action of dose reduced in the AE form, but no corresponding dose reduced due to an AE in the exposure data.

[b] Patient 103-010 had TEAEs with action of dose withheld in the AE form, but no corresponding dose withheld due to AE in the exposure data. Patient 101-093 had dose withheld due to an AE in the exposure data, but no corresponding TEAEs with action of dose withheld in the AE form.

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

[d] Re-escalation after a dose reduction.

Data cutoff date: 24 September 2021.

Adverse events

Table 52. Summary of Treatment-Emergent Adverse Events Tissue-Agnostic and Overall Safety Populations

	Tissue-Agnostic Safety Population N=45	Overall Safety Population N=796
Any TEAE, n (%)	45 (100)	795 (99.9)
Related to selpercatinib	40 (88.9)	756 (95.0)
Grade ≥3 TEAE, n (%)	29 (64.4)	572 (71.9)
Related to selpercatinib	17 (37.8)	307 (38.6)
TE-SAE, n (%)	18 (40.0)	353 (44.3)
Related to selpercatinib	3 (6.7)	87 (10.9)
Fatal TEAE, n (%)	3 (6.7)	45 (5.7)
Related to selpercatinib	0	1 (0.1)
TEAE leading to permanent treatment discontinuation, n (%)	4 (8.9)	64 (8.0)
Related to selpercatinib	1 (2.2)	25 (3.1)

Abbreviations: N = number of patients in the safety population; n = number of patients in the specific category; TEAE = treatment-emergent adverse event; TE-SAE = treatment-emergent serious adverse event.

Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)

Table 53. Treatment-Emergent Adverse Events by Preferred Term and Aggregating Composite Term Occurring in ≥15% Patients in the Tissue-Agnostic Safety Population, any Grade Tissue-Agnostic and Overall Safety Populations

	Tissue-Agnostic Safety Population N=45		Overall Safety Population N=796	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with any selected TEAEs	45 (100.0)	29 (64.4)	795 (99.9)	572 (71.9)
Alanine aminotransferase increased	19 (42.2)	7 (15.6)	284 (35.7)	91 (11.4)
Aspartate aminotransferase increased	17 (37.8)	6 (13.3)	292 (36.7)	70 (8.8)
Dry mouth	15 (33.3)	0	344 (43.2)	0
Abdominal pain	15 (33.3)	4 (8.9)	268 (33.7)	20 (2.5)
Hypertension	14 (31.1)	10 (22.2)	326 (41.0)	157 (19.7)
Fatigue	13 (28.9))	3 (6.7)	365 (45.9)	25 (3.1)
Diarrhoea	13 (28.9)	1 (2.2)	374 (47.0)	40 (5.0)
Oedema	11 (24.4)	0	386 (48.5)	6 (0.8)
Rash	11 (24.4)	0	261 (32.8)	5 (0.6)
Nausea	10 (22.2)	2 (4.4)	248 (31.2)	9 (1.1)
Constipation	10 (22.2)	0	261 (32.8)	6 (0.8)
Blood alkaline phosphatase increased	8 (17.8)	5 (11.1)	116 (14.6)	17 (2.1)
Pyrexia	8 (17.8)	0	135 (17.0)	1 (0.1)
Insomnia	8 (17.8)	0	115 (14.4)	0
Vomiting	7 (15.6)	2 (4.4)	178 (22.4)	14 (1.8)
Electrocardiogram QT prolonged	7 (15.6)	1 (2.2)	168 (21.1)	38 (4.8)
Dyspnoea	8 (17.8)	1 (2.2)	179 (22.5)	25 (3.1)
Blood creatinine increased	7 (15.6)	1 (2.2)	227 (28.5)	15 (1.9)
Headache	7 (15.6)	0	220 (27.6)	11 (1.4)
Back pain	7 (15.6)	0	153 (19.2)	12 (1.5)
Decreased appetite	7 (15.6)	0	150 (18.8)	3 (0.4)
Thrombocytopenia	7 (15.6)	0	123 (15.5)	24 (3.0)

Abbreviations: N = number of patients in the safety population; TEAE = treatment-emergent adverse event.
Notes:

- Adverse events are sorted in descending frequency based on the all-causality count in the **Tissue-Agnostic Safety Population**.
- The component Preferred Terms comprising each composite term (*italicized*) are provided in SCS Appendix Table APP.2.7.4.1.

Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)

A total of 64.4% (n=29) patients in the TA Safety Population and 71.9% (n=572) patients in the Overall Safety Population experienced 1 or more Grade 3 or higher TEAEs of which 37.8% and 38.6% were respectively adjudicated as treatment-related by the Investigator.

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

Serious adverse event/deaths/other significant events

Serious AEs

Table 54. Treatment-Emergent Serious Adverse Events All Causality Occurring in ≥2 Patients in Tissue-Agnostic Safety Population or ≥2% Patients in Overall Safety Population Tissue-Agnostic and Overall Safety Populations

	Tissue-Agnostic Safety Population N=45		Overall Safety Population N=796	
	All Causality, n (%)	Related, n (%)	All Causality, n (%)	Related, n (%)
Patients with treatment-emergent SAEs	**18 (40.0)**	**3 (6.7)**	**353 (44.3)**	**87 (10.9)**
Abdominal pain	2 (4.4)	0	20 (2.5)	3 (0.4)
Nausea	2 (4.4)	0	7 (0.9)	2 (0.3)
Pyrexia	2 (4.4)	0	10 (1.3)	2 (0.3)
Vomiting	2 (4.4)	0	11 (1.4)	1 (0.1)
Hypersensitivity	1 (2.2)	1 (2.2)	16 (2.0)	16 (2.0)
Dyspnoea	1 (2.2)	0	18 (2.3)	0
Hyponatremia	1 (2.2)	0	18 (2.3)	0
Pneumonia	0	0	33 (4.1)	0
Pleural effusion	0	0	24 (3.0)	5 (0.6)

Abbreviations: N = number of patients in the safety population; n = number of patients in the specific category; SAE = serious adverse event.

Notes:

- Adverse events are sorted in descending frequency based on the all-causality count in the **Tissue-Agnostic Safety Population**.
- The component Preferred Terms comprising each composite term (*italicized*) are provided in SCS Appendix Table APP.2.7.4.1.

Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)

In the TA Safety Populations, 40% (n=18) of subjects treated with selpercatinib 160 mg BID experienced a treatment-emergent-SAE (TE-SAEs) and 6.7% were adjudicated as treatment-related by the Investigator. In comparison, in the overall safety population, 44.3% (n=353) of patients treated experienced a TE-SAEs and 10.9% were adjudicated as treatment-related.

The most common TE-SAEs occurring in 2 or more patients in the TA Safety Populations were abdominal pain, nausea, vomiting and pyrexia.

The most common TE-SAEs occurring in 2 or more patients in both the Overall and TA Safety Populations were abdominal pain, nausea, vomiting and pyrexia.

Deaths

Table 55. Summary of Deaths RET-Fusion Positive Safety Analysis Populations

	Tissue-Agnostic Safety Population N=45	Overall Safety Population N=796
Within 28 days of last dose, n (%)	7 (15.6)	56 (7.0)
Disease progression	3 (6.7)	19 (2.4)
Adverse event	3 (6.7)	34 (4.3)
Other	1 (2.2)[a]	3 (0.4)
More than 28 days after last dose, n (%)	12 (26.7)	137 (17.2)
Disease progression	11 (24.4)	109 (13.7)
Adverse event	0	10 (1.3)
Other	1 (2.2)	18 (2.3)

Abbreviations: N = number of patients in the safety population; n = number of patients in the specific category.
[a] Other included: Death due to disease progression and blockage of portal vein.
Note: Percentage is calculated based on the number of patients in the column heading as the denominator.
Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)

In TA safety population a fatal (Grade 5) TEAE was experienced by a total of 19 patients (~42.3%), including 7 patients who died of disease progression (n=3) or AE (n=3) within 28 days of the last dose of selpercatinib.

In the Overall Safety Population, 34 of the 56 deaths within 28 days of the last dose were related to a TEAE; 19 were due to disease progression, and 3 were due to other causes.

Adverse Events of Special Interest

AST/ALT increased

AST and ALT increases were reported in 36.7% and 35.7% of patients in the Overall Safety Population and 37.8% and 42.2% of patients in the TA Safety Population, respectively. Majority were of Grade 1 or 2.

Hypertension

The incidence of any-grade hypertension was reported in 41% of patients in the Overall Safety Population and 31.1% in TA safety population, 19.7% and 22.2% were Grade ≥3 in the Overall and TA Safety Population, respectively. Patients with a documented history of hypertension displayed a higher incidence of treatment-emergent Grade 3 hypertension than patients without (28.2% versus 14.2%, respectively). This trend is the same in the TA safety population (38.2% versus 11.2, respectively).

Hypersensitivity

The overall incidence of any-grade hypersensitivity was 5.9% in the Overall Safety Population and 2.2 in the TA safety population. A total of 15 patients (1.9%) in the Overall Safety and none patients in the TA Safety Population had Grade 3 hypersensitivity.

QT prolongation

Electrocardiogram QT prolonged was reported as a TEAE in similar proportion of the patients in both the Overall (21.1%) and TA (15.6%) Safety Populations. Most patients had TEAEs of Grade 1 or 2 in severity in both the Overall Safety (16.3%) and TA safety (13.3%) population.

Laboratory findings

The highest incidence of any grade treatment-emergent laboratory abnormality across haematology parameters was reported for decreased lymphocyte count (51.8% and 51.2%) and decreased white blood cell count (48.7% and 42.2%) in both the Overall Safety Population and the TA Safety Population, respectively.

The highest incidence of any grade treatment-emergent serum abnormality was reported for AST increased (58.9% and 60.0%) and albumin decreased (55.7% and 48.9%) in both the Overall Safety Population and the TA Safety Population, respectively.

Safety in special populations

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

Discontinuation due to adverse events

The most common reasons for dose interruptions and dose reductions of treatment are related to the investigations SOC for both population, being liver transaminase elevation.

The frequency of dose interruptions, dose reductions and treatment discontinuations due to AEs is lower in the TA safety population (55.6%, 31.1% and 8.8%, respectively) than in the overall safety population (64.2%, 40.7%, and 8% respectively).

Post marketing experience

Selpercatinib was first authorized by the European Commission on 11 February 2021 and has been granted marketing authorization in over 35 countries. Selpercatinib is currently authorized for

- *RET* fusion-positive NSCLC
- *RET* fusion-positive TC, and
- *RET*-mutant MTC.

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

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

2.5.1. Discussion on clinical safety

Safety was evaluated in patients in the Overall Safety Population (N=796) and in the Tissue-Agnostic Safety Population (N=45) who received at least 1 dose of selpercatinib as of the data cut-off 24 September 2021. The overall Safety Population included in the SmPC (837 patients) derives from Procedure EMEA/H/C/005375/R/0026 concluded on 05/01/2024.

Data cut-off date for the Overall Safety Population (n=796) was 15 June 2021. Safety data from this population have been assessed in the previous extension of indication variation procedures EMEA/H/C/005375/II/0011 and EMEA/H/C/005375/II/0014.

Fourteen (14) unique tumour types are represented in the Tissue-Agnostic Safety Population. Two tumour subgroups in the Tissue-Agnostic Population had 5 or more patients: pancreatic cancer and Colorectal Cancer.

The median age (53 years) in the Tissue-Agnostic safety Population is younger than typically observed in cancer studies (59 years). In particular, the pancreatic subpopulation had a median age of 45 years and represents approximately 25% of the Tissue-Agnostic safety Population.

In terms of exposure, the median time on treatment was 21.3 and 6.6 months, respectively, for the Overall Safety Population and Tissue-Agnostic Safety Population. In the tissue-agnostic population, the median treatment duration is 6.6 months (range: 0.6 to 44.0 months) and 91.1% of patients were on treatment for at least 6 months.

The median relative dose intensity was similar for the Overall Safety Population (94.5%) and the TA Safety Population (97.8%).

The most reported dose modification was dose withheld (72.9% in the Overall Safety Population and 62.2% in the Tumor Agnostic Safety Population) primarily attributed to adverse events (AEs) (64.1% in the Overall Safety Population and 55.6% in the overall TA Safety Population).

The frequency of dose interruptions, dose reductions and treatment discontinuations due to AEs is lower in the TA safety population (55.6%, 31.1% and 8.8%, respectively) than in the overall safety population (64.2%, 40.7%, and 8% respectively).

In both the Tissue-Agnostic Safety Population and the Overall Safety Population the most frequent TEAEs considered related to selpercatinib that led to dose withheld or dose reductions were ALT increased and AST increased.

For TEAEs, 45 (100%) patients in the Tissue-Agnostic Safety Population reported any TEAE and in 40 (88.9%) subjects, these events were considered related to selpercatinib. The most commonly reported PTs were ALT and AST increased (42.2% and 37.8% respectively), dry mouth, abdominal pain (33.3% each) and hypertension (31.1%). Grade ≥3 AEs were reported by 29 (64.4%) subjects in the Tissue-agnostic population and, in 17 (37.8%) subjects, the events were considered related to selpercatinib treatment. The most common Grade ≥3 PT was hypertension (22.2%).

Regarding SAEs, these were observed in 18 (40%) patients and were considered related to treatment in three (6.7%) cases that were reported as drug-induced liver injury, fatigue and hypersensitivity.

There were 7 (15.6%) deaths in the TA Safety Population within 28 days of the last dose of selpercatinib. Three (6.7%) of these were due to disease progression and 3 (6.7%) were due to TEAEs that were determined to be unrelated to selpercatinib treatment by the investigator.

Most of the deaths reported more than 28 days after last dose (11/12) were due to disease progression except for one that was reported as due to other reason. The narrative for this subject is not available.

Percentages of deaths were higher in the tissue-agnostic population compared to the overall safety population but comparison is difficult due to the small sample size of the tissue-agnostic group.

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

Identified AESIs for selpercatinib are liver injury (including ALT/AST increased, drug-related hepatic disorders based on SMQs and hepatocellular injury based on Hy's Law), hypertension, drug hypersensitivity and QT prolongation. For most events related to liver injury, reported percentages are higher for the tissue-agnostic population, compared to the overall safety population, but interpretation of these differences is limited by the unbalanced sample sizes. No patients from the tissue-agnostic population met the Hy's Law criteria. Hypertension and hypersensitivity were reported in similar rates in both populations. ECG QT prolongation was observed in seven (15.6%) patients from the tissue-agnostic safety population, only one of them being Grade 3 of severity. One event of ECG QT prolongation led to dose reduction.

The safety profile observed in the data from the 24 September 2021 cut-off and from the 13 January 2023 cut-off (procedure EMEA/H/C/005375/R/0026 concluded on 05/01/2024) remains consistent with previously reported data. No new ADRs or AESIs have been identified since initial authorisation and the safety profile is consistent between the Tissue-Agnostic population and the Overall Safety Population.

2.5.2. Conclusions on clinical safety

The overall safety profile of selpercatinib in the Tissue-Agnostic population 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.

As previously stated for other extension of the indication procedures, safety assessment in the context of a single-arm trial presents several limitations. Sample size in the tissue-agnostic safety population (n=45) is too small and the exposure time (median around 6 months) is short. However, safety results in the overall population (n=796) which has previously been assessed (Retsevmo II-11 and II-14) is considered supportive and sufficient for an initial safety assessment. Considering the available data, and the fact that most patients included in this tissue-agnostic population had received prior treatment lines and had no better treatment options, the toxicity is considered manageable and in line with the previously identified safety aspects.

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 with this application. The (main) proposed RMP changes concerned addition of a new indication for the treatment of adults with advanced or metastatic *RET* fusion-positive solid tumours with disease progression on or after systemic therapies or who have no satisfactory therapeutic options.

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

The PRAC considered that the risk management plan version 3.5 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 8.1 with the following content:

Safety concerns

Table 56. Summary of safety concerns

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

The existing list of safety concerns remain unchanged.

Pharmacovigilance plan

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

Risk minimisation measures

Table 57. Risk minimisation measures

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Liver injury	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Cardiac arrhythmia due to QT prolongation	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Reproductive and developmental toxicity	**Routine risk minimisation measures:** SmPC Section 4.6 **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Pregnancy and Breastfeeding follow-up forms **Additional pharmacovigilance activities:**

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

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

2.7. Update of the Product information

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

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

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 revised indication targets a similar patient demographic group as made up the representative test population for the user testing previously performed.
- The structure and design of the revised Retsevmo Package Leaflet has not changed due to the new information.
- The proposed revisions do not significantly affect the overall readability.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Retsevmo (selpercatinib) is included in the additional monitoring list as New active substance, Conditional marketing authorisation.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication is:

Retsevmo as monotherapy is indicated for the treatment of adults with advanced *RET* fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted (see sections 4.4 and 5.1).

3.1.2. Available therapies and unmet medical need

Selpercatinib is already authorized in the EU for the treatment of adults with:

- advanced *RET* fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor
- advanced *RET* fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib

And for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant medullary thyroid cancer (MTC).

Gavreto (pralsetinib) is a RET inhibitor indicated as monotherapy for the treatment of adult patients with rearranged during transfection (*RET*) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor, i.e. the same indication as selpercatinib in NSCLC.

There is currently no approved treatment in EU targeting specifically *RET* fusion positive cancer other than NSCLC and MTC. For other malignant conditions harbouring *RET*-fusion, there are no treatments specifically directed to this potential driver. Patients are usually treated following the standards of wild-type cancers, highly variable across involved organs (surgical resection, radiation therapy, systemic therapy, or combinations of multiple modalities). Systemic therapies can range from oral tyrosine kinase inhibitors or hormone therapy to immunotherapy to multiagent chemotherapy regimens. Some *RET* fusion-positive solid tumour e.g., cancer of unknown primary origin, certain skin cancers, and histiocytosis may not have established standards of care due to their rarity, and there exists an unmet medical need for relevant treatments.

3.1.3. Main clinical studies

The totality of the data for this submission come from the phase 1/2 LIBRETTO-001 study. The part I was a dose escalation phase in patients with advanced solid tumour with *RET* alterations/activation and the part II was an dose extension phase with 6 different cohorts. Patients included in this submission could potentially be recruited in part I and part II cohort 1 (advance *RET* fusion + solid tumour progressed or intolerant to standard first line therapy), cohort 2 (advance *RET* fusion+ solid tumour without standard first line therapy), cohort 5 (cohort 1-4, disease not measurable) and cohort 6 (patients otherwise eligible for cohort 1-5 who discontinued other RET inhibitors).

At the initial cut-off date (DCO 24 September 2021), 41 patients were evaluable for efficacy in the following *RET* fusion positive solid tumour: pancreatic (n=11), colon (n=10), salivary (n=4), unknown primary (n=3), breast, sarcoma, xanthogranuloma (n=2 each), carcinoid, ovarian, small intestine, cholangiocarcinoma, pulmonary carcinosarcoma, renal neuroendocrine and carcinoma of the skin (n=1 each). Updated efficacy data were provided during the procedure (DCO 13 January 2023) based on 52 efficacy evaluable patients.

3.2. Favourable effects

At the data cut-off 13 January 2023, ORR (95% CI) by IRC in patients with *RET*-fusion positive tumours was 44.2% (30.47, 58.67) and was overall consistent with ORR by INV. Responses were mainly PR (38.5%, 20 patients) and with 5.8% of CR (3 patients). Clinical benefit rate (CR+PR+SD $\geq$ 16 weeks) was evaluated at 67.3% (disease control rate (CR+PR+SD) was 78.0% at DCO 24 September 2021).

Median DoR (95% CI) was 37.19 months (13.3, NE) according to IRC and 18.60 months (9.8, NE) according to investigator's assessment.

Median (min, max) time to response was 1.87 (1.6, 13.6) months according to IRC. In general, time to best response was aligned with TTR.

Objectives responses were observed in several tumour types for which patients have exhausted all available therapeutic options.

3.3. Uncertainties and limitations about favourable effects

The efficacy database is limited (52 patients) with down to one patient in some tumour types, therefore results cannot be considered comprehensive. This is inherent to the low incidence of conditions harbouring RET fusion and recruitment difficulties. The final analysis of the tissue agnostic efficacy set will increase this sample size to 74 patients and will be submitted as specific obligation.

Presented analyses are considered exploratory with a poor justification of the sample size calculation made at a very late stage or the 20% ORR threshold. Subgroup analyses are also limited by the small sample size considering the analysis by tumour type. This is reflected in section 4.4 and 5.1 of the SmPC.

Data provided for this submission originate from a single non-randomized phase I/II study, thus hampering the assessment of time-dependant outcome. Nevertheless, data from 2 RCTs in RET-fusion NSCLC and RET-mutant MTC will provide supportive data with time dependant outcome in clinical settings where the RET alterations are deemed to be the oncogenic driver event and thus the main effect modifier.

3.4. Unfavourable effects

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

At the initial cut-off date 24 September 2021, in the Tissue-Agnostic Safety Population, AEs were reported for all patients (related to selpercatinib per investigator judgment in 88.9%). A total of 64, 4% AEs (causally related according to investigator in 37.8%) were CTCAE grade 3 or higher.

Serious adverse events (SAEs) were reported in 40% (n=18/45) of subjects treated with selpercatinib 110 mg and only 6.7% were adjudicated as treatment-related by the Investigator. The most commonly reported SAEs were abdominal pain, nausea, vomiting and pyrexia.

There were 7 (15.6%) deaths in the TA Safety Population within 28 days of the last dose of selpercatinib. Three (6.7%) of these were due to disease progression and 3 (6.7%) were due to TEAEs that were determined to be unrelated to selpercatinib treatment by the investigator.

Updated DCO for reference (not described extensively in section)

At the latest cut-off date 13 January 2023, in Tissue-Agnostic Safety Population, AEs were reported for all patients (related to selpercatinib per investigator judgement in 90.9%). A total of 72.7% AEs (related according to investigator in 40.0%) were CTCAE grade 3 or higher.

Serious adverse events (SAEs) were reported in 47.3% (n=26/55) subjects treated with selpercatinib 110 mg and only 7.3% were adjudicated as treatment-related by the Investigator. The most commonly reported SAEs were abdominal pain, nausea, vomiting and pyrexia.

There were 9 (16.4%) deaths in the TA Safety Population within 28 days of the last dose of selpercatinib, of which 4 (7.3%) were due to an AE (aspiration, cardiac arrest, dyspnoea, and neoplasm progression) that were determined to be unrelated to selpercatinib treatment by the investigator.

3.5. Uncertainties and limitations about unfavourable effects

As previously stated for other extension of the indication procedures, safety assessment in the context of a single-arm trial presents multiple limitations in terms of causality adjudication and clinical relevance identification, among others. Data on long-term safety in adult will be provided from LIBRETTO-001 final analysis of the tumour agnostic safety population, and in the context of randomized studies study from LIBRETTO-431 and LIBRETTO-531 as specific obligations.

3.6. Effects Table

Table 58. Effects Table for selpercatinib for the Treatment of Patients with RET Fusion-Positive Histology-independent Solid Tumour

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects in the tumour agnostic efficacy population n=52 (DCO 13 January 2023)						
ORR	Rate	n (%) (95% CI)	23 (44.2) (30.47, 58.67)	NA		
DoR	Median	Months (95% CI)	37.19 (13.3,NE)	NA	18.60 (9.8, NE) by INV	
Unfavourable Effects in the TA safety population, N=45 (DCO 24 September 2021)						
AEs grade ≥3	Adverse events grade 3-4	%	64.4%	NA	Absence of comparative data.	Safety section of ARs

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	regardless causality					
SAEs	Serious AEs regardless causality	%	40%	NA		
Deaths	Number of deaths	Absolute value (%)	19 (42.3%)	NA		
QT prolongation	AE of special interest	%	15.6%	NA		
AEs leading to discontinuation		%	8.8%	NA		
AEs leading reductions		%	31.1%	NA		
AEs leading interruptions		%	55.6%	NA		

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

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The MAH is seeking an extension of indication for Retsevmo in patients with advanced or metastatic *RET* fusion-positive solid tumour, i.e. histology independent indication. There are two previous examples of approved marketing authorizations in such histology-independent indication, both in patients with NTRK gene fusion who have no satisfactory therapeutic options: Vitrakvi (larotrectinib) and Rozlytrek (entrectinib). Compared to these examples, the size of efficacy data set is more limited and efficacy results seem less outstanding although the comparison of response tumours harbouring different genetic characteristics is difficult.

Nevertheless, considering the single arm design of the LIBRETTO-001 study, preventing any comparison with standard therapy, and given the last line setting of the included patients, it is considered that efficacy results are promising in patients with no available satisfactory therapeutic option. Selpercatinib has showed an ORR of 44.2% (95% CI: 30.47, 58.67) with a median DoR of 37.19 (95% CI: 13.3, NE) months in patients with RET-fusion positive solid tumours other than NSCLC and TC.

However, the limited sample size (n=52, with n=74 expected at the final analysis) precludes definitive conclusion on efficacy across tumour types with only a single subject in some cases. This can be considered an inherent limitation in the context of applications for histology independent indications. Indeed, due to the low number of patients, efficacy estimates are generally imprecise, with wide confidence intervals.

The wording of the indication was amended to make it clear that Retsevmo is indicated in patients who have no satisfactory treatment options in line with other medicines approved for histology-independent indications. The wording "when treatment options not targeting RET provide limited clinical benefit, or have been exhausted" is meant to clarify that the treatment should not be used in a population that would have already received another RET targeting therapy in an earlier line.

Objective responses were observed in the most represented tumour types (pancreas and colon) and in others represented by 2 to 4 patients. In addition, in half of the tumour types represented by only one patient, objective responses were observed. Retsevmo showed activity in single patient protocol and in literature for additional tumour types. Although evidence of the absence of a potential tissue modifier effect can be challenged, activity results were obtained in more than 20 tumour types with durable responses.

Further, considering the lack of comprehensive data in the sought indication, additional efficacy (and safety) data will be provided as post-approval measure. Indeed, results from 2 RCTs in RET-Fusion NSCLC and RET-mutant MTC will allow to support the demonstration of efficacy in the histology-independent indication and to obtain a higher level of evidence by capturing time to event endpoints.

In addition, consistently with already authorized indications of Retsevmo, median time to response was short (1.8 months) and time to best response align with TTR. Although median DoR as assessed by investigator (18.6 months) was shorter compared to median DoR by IRC (37.19 months), these results are considered clinically relevant in these settings of advanced and metastatic disease, especially in last-line indications.

Despite uncertainties pertaining to the single arm design and the sample size, efficacy results are considered promising in patients who have exhausted all available therapeutic options. Considering the available safety data, and the fact that most patients included in this histology-independent population have received prior treatment lines and have no better treatment options, the toxicity is considered manageable and in line with the previously identified safety profile.

3.7.2. Balance of benefits and risks

Limitations pertaining to the design of the pivotal study and the small sample size that were hampering a proper assessment for a tissue histology independent indication in early treatment lines were addressed by the MAH who discussed a potential tissue modifying effect, see 2.4.2. Discussion on clinical efficacy. In addition, the wording of the indication was revised to reflect a last line setting where benefit can be concluded as demonstrated. Considering that tumour types in which an activity was observed (including RET-fusion NSCLC and TC), are representative of the distribution of RET-fusion positive tumour types (see section 2.1.1), it is considered that the uncertainty relative to the potential tissue modifying effect has been sufficiently addressed, also with regards to the last line setting of the finally agreed indication.

In addition, data from 2 RCTs in RET-Fusion NSCLC and RET-mutant MTC to support the magnitude of the already observed effect in these indications and capturing time to event endpoints will provide a more comprehensive level of evidence, although results in RET-mutant MTC might be of lesser relevance. Finally, a RWE study will be set up to support the histology-independent indication (REC).

Compared to the demonstrated benefits in the last line setting of this histology independent indication, the known and manageable safety profile of Retsevmo is deemed acceptable.

Overall, despite the limitations related to the design and the sample size which do not allow to consider an authorization in early treatment lines, the benefit-risk balance of Retsevmo can be considered positive in a histology independent indication when available treatment options provide limited clinical benefit or have been exhausted.

3.7.3. Additional considerations on the benefit-risk balance

The current dataset for patient in the histology independent indication is 52 patients and based on a single arm study, hampering the assessment of time to event endpoints. This dataset is not considered sufficient to consider the data comprehensive.

The new indication for this product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

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

- The benefit-risk balance is positive, as discussed above.
- It is likely that the applicant will be able to provide comprehensive data.

  The current dataset supporting this histology independent indication comprises 52 patients and the final analysis will provide data of 74 patients. The MAH committed to provide 3 SOBs to confirm the efficacy and safety of Retsevmo in the histology independent indication (final data of LIBRETTO-001 in 74 patients, and results from 2 RCTs in RET-fusion NSCLC in 261 patients and RET-mutant MTC in 291 patients). Comprehensiveness of the data package is expected to be achieved based on the totality of the data to be submitted, including not only the SOBs, but also the data supporting the already authorized indications. This represents more than 1000 patients and is deemed sufficient.
- Unmet medical needs will be addressed, as given the qualification of the indication to patients for which treatment options not targeting RET provide limited clinical benefit, or have been exhausted, it is ascertained that there is an unmet medical need which could be covered by Retsevmo.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required, considering the relevant ORR observed in patients treated with Retsevmo, better than currently recommended standard treatment in earlier lines (see Table 1), the last line setting in patients with an unmet medical need and the known and manageable safety profile of Retsevmo.

3.8. Conclusions

The overall B/R of Retsevmo for the treatment of adults with advanced RET fusion positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 28 out of 30 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication for RETSEVMO to include the treatment of adults with advanced RET fusion positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted, based on interim data from study LIBRETTO-001 (LOXO-RET-17001); LIBRETTO-001 is an open-label, multicentre, global Phase 1/2 study of selpercatinib in in adult and adolescent patients with advanced RET-altered tumours. As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP has been agreed. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

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, II and IIIB and to the Risk Management Plan are recommended.

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

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

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive non-small cell lung cancer, the MAH should submit the clinical study report of the Phase 3 study J2G-MC-JZJC (LIBRETTO-431) comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC. The CSR should be submitted by	31 December 2024
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET-mutant medullary thyroid carcinoma, the MAH should submit the clinical study report of the Phase 3 study J2G-MC-JZJB (LIBRETTO-531) comparing selpercatinib to physician's choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naive, RET-mutant MTC. The CSR should be submitted by	30 September 2025
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive solid tumours other than NSCLC and thyroid cancer, the MAH should submit the final data from patients with RET-fusion positive solid	31 December 2025

Description	Due date
tumours other than NSCLC and thyroid cancer enrolled in the pivotal study LIBRETTO-001.	

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Retsevmo is not similar to Nexavar, Lutathera, Onivyde, Zejula, Pemazyre, Kimmtrak, Xermelo, Qarziba, Ayvakyt, Kosulego, Somakit, Qinlock, Crysvita, Cometriq, Tibsovo, Finlee and Spexotras within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. Appendices

5.1. Divergent position to the majority recommendation

APPENDIX

DIVERGENT POSITION

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the approval of the following indication in the context of the conditional marketing authorisation of Retsevmo (selpercatinib):

Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive solid tumours when treatment options not targeting RET provide limited clinical benefit, or have been exhausted.

The reasons for divergent opinion were the following:

The overall data package is too limited to conclude that the results represent clinical benefit across the target population, thus it is not considered sufficient to support the sought broad site - and histology - independent indication. Half of the dataset is represented by two tumor types only (pancreatic and colon cancer), which have different ORR estimates, also in relation to the already approved Retsevmo (selpercatinib) indications in specific tumor types (i.e., RET-fusion positive NSCLC and RET-fusion positive thyroid cancer), further questioning the homogeneity of treatment effect regardless histology. The plan to generate post-approval data related to a full histology-independent indication in the context of a clinical trial setting is rather limited (LIBRETTO-001 already closed to enrolment and characterized by an exploratory and adaptive nature), further the unclear plan on real world data raise doubt on its utility post-approval.

In conclusion, while the safety profile is deemed manageable, there is such an uncertainty on the observed activity which does not allow to conclude on a positive B/R on a broad site- and histology- independent indication (i.e., adults with advanced RET fusion-positive solid tumours when treatment options not targeting RET provide limited clinical benefit, or have been exhausted).

CHMP Members expressing a divergent opinion:

Paolo Gasparini – IT

Peter Mol – NL