swissmedic

Date: 9 July 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

RETSEVMO

International non-proprietary name:	selpercatinib
Pharmaceutical form:	hard capsules
Dosage strength(s):	Retsevmo 80 mg, gélules, Retsevmo 40 mg, gélules
Route(s) of administration:	oral
Marketing authorisation holder:	Eli Lilly (Suisse) SA
Marketing authorisation no.:	67862
Decision and decision date:	extension of therapeutic indication as a temporary authorisation in accordance with Art. 9a TPA approved on 21 March 2025 and extension of therapeutic indication approved on 21 March 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BICR	Blinded independent review committee
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
HR	Hazard Ratio
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MKI	Multikinase inhibitor
MTC	Medullary thyroid carcinoma
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)

PTC	Papillary thyroid carcinoma
RET	REarranged during Transfection
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 16 December 2021.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

Temporary authorisation for human medicinal products
The applicant requested temporary authorisation in accordance with Article 9*a* TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Indications subject to temporary authorisation

Retsevmo as monotherapy is indicated for the treatment of adults with:
- advanced RET fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor
- advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib

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

2.2.2 Approved indication

Indications subject to ordinary authorisation

Retsevmo as monotherapy is indicated
- For the treatment of adults and adolescents of 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) (see "Warnings and precautions" and "Clinical efficacy")

Indications subject to temporary authorisation

Retsevmo as monotherapy is indicated for the first-line treatment of adults with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) *(see* "Properties/effects").

The efficacy and safety of Retsevmo in patients with additional oncogenic driver mutations have not been evaluated (see "Warnings and precautions").

Since the documentation was incomplete at the time the application was assessed, this indication is approved for a limited period (Art. 9a of the Therapeutic Products Act). This temporary authorisation is contingent on the timely fulfilment of conditions. After these have been met, the temporary approval can be converted into an approval without special conditions.

2.2.3 Requested dosage

Summary of the requested standard dosage:

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	25 April 2023
List of Questions (LoQ)	10 August 2023
Response to LoQ	29 October 2023
Second LoQ	11 December 2023
Response to second LoQ	29 February 2024
Preliminary decision	28 May 2024
Response to preliminary decision	16 August 2024
Labelling corrections and/or other aspects	07 October 2024
Response to labelling corrections and/or other aspects	07 November 2024
Second labelling corrections and/or other aspects	19 December 2024
Labelling meeting	16 January 2025
Response to second labelling corrections and/or other aspects	03 February 2025
Final decision	21 March 2025
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority EMA. This SwissPAR relates to the publicly available assessment reports for Retsevmo, published on 22 April 2022, Procedure No. EMEA/H/C/005375/II/0011, and 22 July 2022, Procedure No. EMEA/H/C/005375/II/0014/G, issued by EMA.

3 Medical context

RET (REarranged during Transfection) is a receptor tyrosine kinase (RTK) involved in the development and maintenance of neural crest-derived cells, including components of the neural and neuroendocrine systems, as well as in kidney development, hematopoiesis, and spermatogenesis. Alterations in the RET gene, such as activating point mutations or gene rearrangements, can lead to constitutive activation of the kinase, promoting uncontrolled cell growth. Selpercatinib is a selective inhibitor of RET.

RET fusion-positive non–small cell lung cancer (NSCLC)
Lung cancer is the leading cause of cancer-related mortality globally. NSCLC accounts for 85% of all lung cancers, with adenocarcinoma being the most common histological subtype (1). The estimated five-year survival rate in metastatic NSCLC is around 9% (2)
RET rearrangements occur in 1%–2% of all NSCLCs, predominantly among younger, non-smoking patients with adenocarcinoma histology (1).
Patients with RET-driven NSCLC are currently treated with the current standard of care for first-line NSCLC (chemotherapy, immune checkpoint inhibitors) regardless of the presence of RET mutation.

RET-mutant Medullary Thyroid Carcinoma (MTC)
MTC is a rare subtype of thyroid cancer, comprising approximately 3% to 5% of all thyroid cancers. A significant proportion of cases are diagnosed at an advanced stage, and the estimated five-year survival rate is approximately 86%, while the ten-year survival rate ranges from 50% to 65% (3).
Activating mutations in the RET gene are the main driver mutation in MTC. Approximately 50% of sporadic forms carry a somatic RET mutation, and familial cases have an identifiable germline mutation in at least 90% of cases (1). RET mutations confer a poor prognosis in MTC (4).
Complete surgical resection remains the only curative approach for locoregional MTC. In cases of recurrent or metastatic disease, treatment options may include surgical resection, external beam radiation therapy, locally directed therapies, or systemic therapies (5).
There are no RET-specific inhibitors authorised for the treatment of first-line RET-mutant MTC. The multikinase inhibitor vandetanib is approved for the treatment of adult patients with unresectable, locally advanced, or metastatic MTC harboring RET mutations.

1) Hoe HJ, Solomon BJ. Treatment of non–small cell lung cancer with RET rearrangements. Cancer. 2025; e35779. doi:10.1002/cncr.35779.
2) Wang Y, Kondrat K, Adhikari J, Nguyen Q, Yu Q, Uprety D. Survival trends among patients with metastatic non-small cell lung cancer before and after the approval of immunotherapy in the United States: A Surveillance, Epidemiology, and End Results database-based study. Cancer. 2025 Jan 1;131(1):e35476. doi:10.1002/cncr.35476. PMID: 38985895.
3) Viola D, Elisei R. Management of medullary thyroid cancer. Endocrinol Metab Clin North Am. 2019 Mar;48(1):285–301. doi:10.1016/j.ecl.2018.11.006. PMID: 30717909.
4) Elisei R, Cosci B, Romei C, Bottici V, Renzini G, Molinaro E, Agate L, Vivaldi A, Faviana P, Basolo F, Miccoli P, Berti P, Pacini F, Pinchera A. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. J Clin Endocrinol Metab. 2008 Mar;93(3):682–7. doi:10.1210/jc.2007-1714. PMID: 18073307.
5) Kim M, Kim BH. Current guidelines for management of medullary thyroid carcinoma. Endocrinol Metab (Seoul). 2021 Jun;36(3):514–524. doi:10.3803/EnM.2021.1082. PMID: 34154310; PMCID: PMC8258323

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment reports for Retsevmo, published on 22 April 2022, Procedure No. EMEA/H/C/005375/II/0011, and 22 July 2022, Procedure No. EMEA/H/C/005375/II/0014/G, issued by EMA.

5 Clinical aspects

5.1 Clinical pharmacology

The evaluation of the clinical pharmacology data for this application relied on previous regulatory decisions by EMA and the US FDA. The available assessment reports and the Summary of Product Characteristics from EMA and the Prescribing Information from the US FDA were used as a basis for evaluating clinical pharmacology. For further details on clinical pharmacology, please see section 8 of this report.

5.2 Dose finding and dose recommendation

No new dose-finding outcomes have been submitted. The proposed dosage aligns with the currently approved regimen for both adults and adolescent patients aged 12 years and older.

5.3 Efficacy

Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority EMA. This SwissPAR relates to the publicly available assessment reports Retsevmo Procedure No. EMEA/H/C/005375/0011 (dated 22 April 2022) and Retsevmo Procedure No. EMEA/H/C/0053I75/II/0014/G (dated 21 July 2022), issued by EMA.
The clinical evaluation focused on the evaluation of the new phase 3 studies LIBRETTO-431 and LIBRETTO-531. Additional results from LIBRETTO-001 are supportive.

RET fusion-positive NSCLC
The Applicant submitted the results of study LIBRETTO-431, a multicentre, randomised, open-label phase 3 trial in patients with RET fusion-positive NSCLC. Adult patients with histologically confirmed, unresectable, locally advanced or metastatic NSCLC who had not received prior systemic therapy for metastatic disease were eligible. Patients with previous neoadjuvant or adjuvant systemic therapy were included if treatment had been completed at least six months prior to randomisation. Patients with squamous histology or significant cardiovascular disease were excluded.

Patients were randomised to receive either selpercatinib at a starting dose of 160 mg twice daily or platinum-based chemotherapy with pemetrexed, with or without pembrolizumab, based on the investigator's intent (Intention to Treat (ITT) population). After 4 cycles of chemotherapy without progressive disease, patients randomly assigned to the control arm received maintenance therapy with pemetrexed with or without pembrolizumab. For details of dosing please refer to the attached Information for healthcare professionals.
Patients assigned to the selpercatinib arm whose disease progressed were allowed to continue treatment with selpercatinib if they were deriving clinical benefit, as determined by the investigator and if approved by the sponsor.
Patients randomly assigned to the control arm were allowed to cross over to selpercatinib treatment upon confirmation of disease progression by a blinded independent review committee (BICR) if they met the eligibility criteria for crossover.
RET fusion status was confirmed prospectively using next-generation sequencing or polymerase chain reaction.
Stratification was based on geographic region, presence of central nervous system metastases at baseline and investigator intent to use pembrolizumab.

The primary endpoints were progression free survival (PFS) as determined by BICR with selpercatinib in the ITT pembrolizumab population and in the ITT population. If statistical significance was reached for both primary endpoints, overall survival (OS) in the ITT population was planned to be tested as secondary endpoint.

A total of 261 patients were included in the ITT population. The median age was 62.5 years, and 54.8% of patients were female. Most patients were of Asian (57.4%) or white (40.2%) ethnicity, and 67.4% were never-smokers. At study entry, 93.5% of patients had metastatic disease, 6.5% were in stage III (17 patients) and 19.5% had CNS metastases. Most patients (96.9%) had an ECOG performance status (PS) of 0 or 1, while 3.1% had a PS of 2.
Of the 261 patients in the ITT population, 212 were included in the ITT pembrolizumab population based on pre-randomisation intent to use pembrolizumab. In this subgroup, 129 patients received selpercatinib, while 83 patients received chemotherapy with pemetrexed and pembrolizumab. Please refer to the attached Information for healthcare professionals for more details regarding the baseline characteristics of the ITT pembrolizumab population.

At the prespecified interim analysis (IA1) for PFS with data cut-off (DCO) date of 1 May 2023, median PFS in the ITT pembrolizumab population was 24.84 months (95% CI: 16.89 to not estimable [NE]) for selpercatinib versus 11.17 months (95% CI: 8.77 to 16.76) for the control arm, with a hazard ratio (HR) for disease progression or death of 0.465 (95% CI: 0.309 to 0.699; p = 0.0002) (statistically significant).
In the ITT population, median PFS was 24.84 months (95% CI: 17.31 to NE) for selpercatinib versus 11.17 months (95% CI: 8.77 to 16.76) for the control arm, with an HR of 0.482 (95% CI: 0.331 to 0.700; p = 0.0001) (statistically significant). In both the ITT and ITT pembrolizumab populations, the Kaplan-Meier curves for selpercatinib and the control arm diverge early and remain consistently separated throughout the entire follow-up period.

At the time of the IA1, OS data were not mature; the analysis did not meet the boundaries for statistical significance. A descriptive IA2 was conducted on 1 May 2024, when 43% of the planned OS events had occurred in the ITT population, reported 75 events across both treatment arms: 49 events (31% of the ITT population) in the selpercatinib arm and 26 events (25%) in the control arm. The estimated OS HR was 1.259 (95% CI: 0.777 to 2.040). As regards post-progression treatments, of the 68 patients in the control arm who experienced disease progression, 74% (n = 50) crossed over to receive selpercatinib. Among the 71 patients in the selpercatinib arm with disease progression, 23% (n = 16) received chemotherapy or immune checkpoint inhibitors, and 62% (n = 44) continued selpercatinib therapy beyond progression. Please refer to the attached Information for healthcare professionals for the OS Kaplan Meier curve.

RET-mutant MTC
The applicant submitted the results of the LIBRETTO-531 trial, a multicentre, randomised, open-label, phase 3 study.

Eligible participants included adult and adolescent patients older than 12 years with histologically confirmed, unresectable, locally advanced or metastatic MTC who had not previously received treatment with a kinase inhibitor for advanced/metastatic disease.
Although the inclusion criteria only required no prior treatment with kinase inhibitors, the extension to the first-line treatment as reported in the requested indication is acceptable as kinase inhibitors are the standard of care in the first-line setting for MTC.
At screening, patients were required to have radiologic disease progression as determined by comparison with an imaging scan taken within the previous 14 months. Patients with significant cardiovascular disease were excluded.

Patients received either 160 mg selpercatinib twice daily or, at the investigator's discretion, 140 mg cabozantinib once daily or 300 mg vandetanib once daily.
Paediatric patients (between 12 and 18 years old) received either 92 mg/m2 selpercatinib twice daily or, at the investigator's discretion, 40 mg/m2 cabozantinib once daily or vandetanib per dosing guide. For details on dosing please refer to the attached Information for healthcare professionals.

In the event of disease progression, patients assigned to selpercatinib were allowed to continue treatment if they were deriving clinical benefit from selpercatinib, as determined by the investigator and if approved by the sponsor.
Patients randomly assigned to the control arm were allowed to cross over to selpercatinib treatment upon confirmation of disease progression by BICR.

RET mutations were prospectively confirmed using next-generation sequencing or polymerase chain reaction. Patients were stratified by RET mutation type, and by intended treatment within the control arm.
The primary efficacy endpoint was PFS as assessed by BICR. Key secondary efficacy endpoints included treatment-failure-free survival (TFFS) and tolerability. OS was also assessed as a secondary endpoint, but was not powered and not under family-wise type I error.

A total of 291 patients were enrolled and randomised in the ITT population: 193 to the selpercatinib arm and 98 to the control arm. Of those in the control arm, 73 were assigned to cabozantinib and 25 to vandetanib. The median age in the ITT population was 55 years. The study included 37.1% female patients. Overall, 69.4% of patients were white, 27.7% Asian, and 2.9% black. ECOG PS was 0–1 in 98.3% of patients and 2 in 1. For details please refer to the attached Information for healthcare professionals.

At the time of the preplanned IA1 with a DCO date of 22 May 2023, the study met its primary endpoint, demonstrating a significant improvement in PFS in the ITT population. At a median follow-up of 12 months, median PFS with selpercatinib had not yet been reached, compared to 16.8 months (95% CI: 12.22 to 25.10) in the control group. The PFS HR was 0.280 (95% CI: 0.165 to 0.475; p<0.0001).

Median TFFS with selpercatinib was also not reached, compared to 13.9 months in the control group. There were 27 TFFS events in the selpercatinib arm and 37 in the control arm, with a HR of 0.254 (95% CI: 0.153 to 0.423; p<0.0001).

In an additional OS analysis with a DCO date of 11 March 2024, with median follow-up of 25 months, 26 OS events had occurred, with 10 (5.2%) events in the selpercatinib arm and 16 (16.3%) in the control arm; the OS results are still immature. The OS HR was 0.275 (95% CI: 0.124 to 0.608).
The updated PFS HR at this time point was 0.202 (95% CI: 0.128 to 0.320).
Adolescent population

The evidence for the efficacy of selpercatinib in the adolescent population is limited. Only one patient under the age of 18 with treatment-naïve MTC was enrolled in the LIBRETTO-531 study. Additionally, results are available from a total of three patients in the phase 1 /2 LIBRETTO-001 study, of whom two had treatment-naïve MTC. Furthermore, data from a total of 14 paediatric patients with MTC are included from the phase 1/2 study LIBRETTO-121. The overall response rate (ORR) for patients with MTC in LIBRETTO-121 was 42.9% (95% CI: 17.7%–71.1%) in the RET-mutant MTC population.

It is noteworthy that a dosage of 92 mg/kg was administered to paediatric patients aged between 12 and 18 in the pivotal study LIBRETTO-531 and in LIBRETTO-121. Although the currently approved dosage in the paediatric population is acceptable, the Information for healthcare professionals has been amended to reflect the fact that the evidence on paediatric patients was limited and based on a dosage of 92 mg/m2.

5.4 Safety

RET fusion-positive NSCLC

Safety was assessed in the safety-overall population of LIBRETTO-531, which included all patients who received at least one dose of study treatment (158 in the selpercatinib arm; 98 in the control arm).

The most frequently reported any-grade treatment emergent adverse events (TEAEs) in the selpercatinib arm included increased AST and ALT hypertension, diarrhoea, oedema, dry mouth, increased bilirubin, rash, fatigue, thrombocytopenia, abdominal pain, leukopenia, increased blood creatinine, neutropenia, constipation and ECG QT prolongation.
Grade ≥3 TEAEs were observed in 72.8% of patients in the selpercatinib arm and 58.2% in the control arm. The most frequent grade ≥3 TEAEs were increased ALT, hypertension, increased AST and prolonged ECG QT.
Serious Adverse Events (SAEs) were reported in 38.9% of patients in the selpercatinib arm vs 24.5% in the control arm. The most frequently reported SAEs (≥2%) in the selpercatinib arm included pleural effusion and hepatic function abnormalities.
A total of 12 grade 5 TEAEs were observed and 9 grade 5 TEAEs occurred in patients treated with selpercatinib on treatment or within 30 days of discontinuation (2 patients died due to myocardial infarction, 1 due to acute respiratory failure, 1 due to cardiac arrest, 1 due to malnutrition, 1 due to sudden death, 1 due to respiratory failure, 1 due to suicide, 1 “death”), 2 occurred during crossover to selpercatinib (1 due to respiratory failure, 1 due to sudden death), and 1 in the control arm. The rate of fatal TEAEs in the control arm was 1.0%.

RET-mutant MTC

At the DCO date of the IA1 in study LIBRETTO-531, TEAEs were reported in 96.4% of patients treated with selpercatinib and 99.0% of patients in the control arm. The most common TEAEs in the selpercatinib arm included hypertension, diarrhoea, increased ALT, increased AST, dry mouth, headache, fatigue and constipation.
Grade ≥3 TEAEs occurred in 52.8% of patients in the selpercatinib arm and 76.3% in the control arm. The most common grade ≥3 TEAEs in the selpercatinib arm included hypertension, increased ALT, fatigue, and diarrhoea.
SAEs were reported in 21.8% of patients in the selpercatinib arm and 26.8% in the control arm.
TEAEs leading to permanent treatment discontinuation occurred in 4.7% of patients in the selpercatinib arm compared to 26.8% in the control arm. On-treatment grade 5 TEAEs occurred in 4 patients (2.1%) in the selpercatinib arm and in 2 patients (2.1%) in the control arm. The causes of the grade 5 TEAEs in the selpercatinib arm were diabetic ketoacidosis, COVID-19, multiple organ dysfunction syndrome and sudden death.

At the DCO date of the IA2, a new signal for erectile dysfunction was identified, which was reported in 15.7% of patients in the selpercatinib arm and 0% in the control arm and has been included in the Information for healthcare professionals.

Adolescent population

The evidence for the safety of selpercatinib in the adolescent population is limited. Safety data in the adolescent population are available from the LIBRETTO-001, LIBRETTO-121 and LIBRETTO-531 studies. The most common TEAEs in LIBRETTO-121 study were diarrhoea, pyrexia nausea, abdominal pain, headache, increased AST levels, increased ALT levels, coronavirus infection, cough, epistaxis and vomiting. Grade ≥3 TEAEs occurred in 57.6% of patients. The most common grade ≥3 TEAEs were weight gain, vomiting, increased ALT, constipation, hypokalaemia and decreased neutrophil count. SAEs occurred in 42.4% of patients. The most common SAE was vomiting. No fatal events were reported.

A safety signal for slipped upper femoral epiphysis was reported in association with selpercatinib in paediatric patients (1 patient in LIBRETTO-121 study, 1 patient in LIBRETTO-531 study, and 1 patient from expanded access). A specific warning regarding this risk was included in the Information for healthcare professionals.

5.5 Final clinical benefit risk assessment

RET fusion-positive NSCLC
The LIBRETTO-431 trial demonstrated a statistically significant and clinically meaningful PFS benefit for selpercatinib compared to the standard of care in NSCLC. However, in first-line treatment, PFS must be interpreted in conjunction with the clinically relevant endpoint OS. At the most recent IA2, OS data were immature, and no statistically significant OS benefit was observed. In addition, the OS HR was >1 with multiple crossing of the curve. In addition, selpercatinib treatment was associated with higher toxicity than the current standard of care. Therefore, on the basis of the data at hand, the benefit was regarded as negative for authorisation without special conditions.

Taking into account the high rate of crossover and the absence of an alternative targeted therapy in this setting, the benefit risk was regarded as positive for a temporary authorisation “ex-officio” according to Art. 18 TPLO. Additional follow-up data and safety analyses from LIBRETTO-431 study were accepted as a condition and must be submitted within the timeframe of temporary authorisation.

RET-mutant MTC
The LIBRETTO-531 study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS, as assessed by BICR, for selpercatinib compared to cabozantinib or vandetanib. OS data are immature and interpretation is limited due to the high censoring rate. However, no detriment was shown for selpercatinib.
Selpercatinib was associated with a lower rate of ≥grade 3 TEAEs, SAEs, grade 5 TEAEs and TEAEs leading to discontinuation compared to cabozantinib or vandetanib.

The efficacy and safety data in the adolescent population are limited. However, taking into account the high unmet medical need in this population and the fact that the limited data are adequately reflected in the Information for healthcare professionals, authorisation in this population was accepted.

Taken together, the overall benefit-risk profile is positive for selpercatinib in the first-line treatment of RET-mutant MTC for patients 12 years and older.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Retsevmo was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ *This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.*

Retsevmo has temporarily authorized indications, see section «Indications/ Uses».

RETSEVMO®

Composition

Active substances

Selpercatinib

Excipients

Microcrystalline cellulose, colloidal Silica

Retsevmo
40 mg Capsule Shell Composition
Gelatin, titanium dioxide (E171), black Iron Oxide (E172)

Retsevmo 80 mg Capsule Shell Composition
Gelatin, titanium dioxide (E171), Brilliant Blue FCF (E133)

Retsevmo Capsules Black Ink Composition
Shellac, propylene glycol, potassium hydroxide, *black* iron oxide *(E172)*

Pharmaceutical form and active substance quantity per unit

Hard capsule.

Retsevmo 40 mg hard capsules:
Each hard capsule contains 40 mg selpercatinib.
Gray opaque capsule, size 2, with ”Lilly”, “3977” and “40 mg” black printing on body of capsule.

Retsevmo 80 mg hard capsules:
Each hard capsule contains 80 mg selpercatinib.
Light blue opaque capsule, size 0, with ”Lilly” “2980” and “80 mg” black printing on body of capsule.

Indications/Uses

Indications with ordinary authorization

Retsevmo as monotherapy is indicated

- For the treatment of adults with metastatic RET-fusion positive non-small-cell lung cancer (NSCLC) who need systemic therapy and have progressed after previous treatment (see «Clinical efficacy»).
- For the treatment of adults with advanced RET-fusion positive papillary thyroid cancer, who need systemic therapy and have progressed after previous treatment including radioiodine (see «Clinical efficacy»).
- For the treatment of adults and adolescents of 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) (see "*Warnings and precautions*" and "*clinical efficacy*")

*Indications with temporary authorization*Retsevmo as monotherapy is indicated for the first-line treatment of adults with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) *(see "properties/effects").*

The efficacy and safety of Retsevmo in patients with additional oncogenic driver mutations have not been evaluated (see «Warning and precautions»).

Due to incomplete documentation at the time of the application being assessed, this indication is approved for a limited period (Art. 9a of the Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After these have been met, the temporary approval can be converted into an approval without special conditions.

Dosage/Administration

Initiation of treatment

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

The presence of a *RET* gene fusion (NSCLC and non-medullary thyroid cancer) or mutation (MTC) should be confirmed with a validated assay for RET-fusions and RET-mutations, prior to initiation of treatment with Retsevmo (see "*clinical efficacy*").

Usual dosage

The recommended dosage of Retsevmo based on body weight is:

- Less than 50 kg: 120 mg
- 50 kg or greater: 160 mg

Take Retsevmo orally twice daily (approximately every 12 hours) until disease progression or unacceptable toxicity.

Dose adjustment following undesirable effects/interactions

Management of some adverse reactions may require dose interruption and/or dose reduction. Retsevmo dose modifications are summarised in Table 1.

Table 1 Recommended Dose Modifications for Retsevmo for Adverse Reactions

Dose Reduction	Patients Weighing Less Than 50 kg	Patients Weighing 50 kg or Greater
First	80 mg orally twice daily	120 mg orally twice daily
Second	40 mg orally twice daily	80 mg orally twice daily
Third	40 mg orally once daily	40 mg orally twice daily

Permanently discontinue Retsevmo in patients unable to tolerate three dose reductions.

The recommended dosage modifications for adverse reactions are provided in Table 2.

Table 2. Recommended dosage in patients Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Hepatotoxicity *(see Warnings and Precautions)*	Grade 3 or Grade 4	• Withhold selpercatinib and monitor AST/ALT once weekly until resolution to Grade 1 or baseline. • Resume at reduced dose by 2 dose levels and monitor AST and ALT once weekly until 4 weeks after reaching dose taken prior to the onset of Grade 3 or 4 increased AST or ALT. • Increase dose by 1 dose level after a minimum of 2 weeks without recurrent increased ALT or AST and then increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT after a minimum of 4 weeks without recurrence. • Permanently discontinue selpercatinib if Grade 3 or 4 ALT or AST increases recur despite dose modifications.
Hypertension *(see Warnings and Precautions)]*	Grade 3	• Withhold selpercatinib for Grade 3 hypertension that persists despite optimal antihypertensive therapy. • Resume at a reduced dose when hypertension is controlled.
	Grade 4	• Discontinue selpercatinib.
	Grade 3	• Withhold selpercatinib until recovery to baseline or Grade 0 or 1.

Adverse Reaction	Severity	Dosage Modification
QT Interval (Prolongation *see Warnings and Precautions)*		• Resume at a reduced dose.
	Grade 4	• Discontinue selpercatinib.
Interstitial Lung Disease/Pneumonitis	Grade 2	• Withhold administration of selpercatinib until the events subsides. To resume, reduce the dose as stated in table 1. • In recurrent ILD/pneumonitis permanently discontinue selpercatinib
	Grade 3 or 4	For Grade 3 or 4, discontinue selpercatinib.
Hemorrhagic Events *(see Warnings and Precautions)*	Grade 3 or Grade 4	• Withhold selpercatinib until recovery to baseline or Grade 0 or 1. • Discontinue selpercatinib for severe or life-threatening hemorrhagic events.
Hypersensitivity Reactions *(see Warnings and Precautions)*	All Grades	• Withhold selpercatinib until resolution of the event. Initiate corticosteroids. • Resume at a reduced dose by 3 dose levels while continuing corticosteroids. • Increase dose by 1 dose level each week until the dose taken prior to the onset of hypersensitivity is reached, then taper corticosteroids.
Other Adverse Reactions (*see Adverse Reactions)*	Grade 3 or Grade 4	• Withhold selpercatinib until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose.

Hypertension

Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled with antihypertensive therapy (see “Warnings and precautions”).

CYP inhibitors

Avoid concomitant use of strong and moderate CYP3A inhibitors with selpercatinib. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the selpercatinib dose as recommended in Table 3. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume selpercatinib at the dose taken prior to initiating the CYP3A inhibitor (see chapter *Interactions*).

Table 3. Recommended Dosage for Concomitant Use of Strong and Moderate CYP3A Inhibitors

	Recommended Retsevmo Dosage	
Current Retsevmo Dosage	**Moderate CYP3A Inhibitor**	**Strong CYP3A Inhibitor**
120 mg orally twice daily	80 mg orally twice daily	40 mg orally twice daily

160 mg orally twice daily	120 mg orally twice daily	80 mg orally twice daily

CYP inducers

Concomitant use of strong and moderate CYP inducers should be avoided (see “Interactions”).

Medicinal products with impact on gastric pH

Concomitant use of selpercatinib with proton pump inhibitors, H2 receptor antagonists or antacids with local effect should be avoided. If however the concomitant use cannot be avoided, the following recommendations for administration have to be considered.

Proton pump inhibitors

Concomitant use of a proton pump inhibitor must be accompanied by a meal (see “Interactions”).

H_2 receptor antagonists

Retsevmo should be administered 2 hours before concomitant H_2 receptor antagonists (see “Interactions”).

Antacids with local effect

Selpercatinib must be taken 2 hours before or 2 hours after administraton of an antacid with local effect (see «Interactions»)

Patients with impaired hepatic function

In patients with mild to moderate hepatic impairment (total bilirubin $\leq$ ULN (upper limit of normal) with AST > ULN or total bilirubin > 1 to 3 x ULN, regardless of AST) a dose adjustment is not required. In patients with severe hepatic impairment [total bilirubin > 3 to 10 x ULN, regardless of AST) should receive a reduced dose of 80 mg twice daily (see «Pharmacokinetics»)

Reduce the recommended dosage of Retsevmo for patients with severe hepatic impairment as recommended in Table 4.

Table 4 Recommended Retsevmo Dosage for Severe Hepatic Impairment

Current Retsevmo Dosage	**Recommended Retsevmo Dosage**
120 mg orally twice daily	80 mg orally twice daily
160 mg orally twice daily	80 mg orally twice daily

Patients with impaired renal function

In patients with mild, (estimated Glomerular Filtration Rate (eGFR) calculated based on Modification of Diet in Renal Disease (MDRD) equation ≥60 and <90 mL/min/1.73 m2), moderate (eGFR ≥30 and <60 mL/min/1.73 m2), or severe (eGFR ≥15 and <30 mL/min/1.73 m2) renal impairment (a dose adjustment is not required. There are no data in patients with end stage renal disease, or in patients on dialysis. (see «Pharmacokinetics»).

Elderly patients

No dose adjustment is required based on age (see “Pharmacokinetics”).

Children and adolescents

Retsevmo should not be used in children aged less than 12 years.

There is no data in children or adolescents with RET fusion-positive NSCLC or thyroid cancer.

In RET-mutant MTC, there are very limited data available in children or adolescents aged less than 18 years (see “*Pharmacodynamic*”, “*Undesirable effects*” and “*Clinical efficacy*”). In most pediatric patients, a dosage of 92 mg/m2 based on body surface area was evaluated. Patients should be dosed according to body weight (see “*Dosage/Administration and pharmacokinetics section*”).

Monitor growth plates in adolescent patients with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment (see “*Warning section”*).

Mode of administration

For oral use.
The capsule should be swallowed whole (patients should not open, crush, or chew the capsule before swallowing), and can be taken with or without food.

Patients should take the doses at approximately the same times every day. Do not take a missed dose unless it is more than 6 hours until next scheduled dose.
If a patient vomits or misses a dose of Retsevmo, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in “Composition”.

Warnings and precautions

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease and/or pneumonitis, including severe, life-threatening and fatal disease, was reported in patients receiving selpercatinib (see Undesirable Effects). Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. In patients with acute or increasing respiratory symptoms that suggest ILD (such as dyspnoea, cough and fever) the administration of selpercatinib has to be withheld and the patient has to be examined prompty for presence of ILD. Based on the severity of ILD/pneumonitis, selpercatinib may require dose interruption, dose reduction, or permanent discontinuation (see Dosage/Administration).

Tumour lysis syndrome (TLS)

Cases of TLS have been observed in patients treated with selpercatinib. Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated as clinically indicated, and appropriate prophylaxis including hydration should be considered.

Increased ALT/AST

Grade ≥3 increased ALT and Grade ≥3 increased AST were reported in patients receiving selpercatinib in clinical trials. (see "Undesirable effects"). Concomitant increases in AST/ALT (≥ 3x ULN) and Bilirubin (≥2x ULN) without findings of cholestasis (elevated serum ALP) were observed in 6 patients in the clinical program.

Monitor ALT and AST prior to initiating selpercatinib, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retsevmo based on the severity (see “Dosage/Administration”).

Hypertension

Hypertension was reported in patients receiving selpercatinib in clinical trials (see "Undesirable effects"). Patient blood pressure is to be controlled before starting selpercatinib treatment. Do not initiate selpercatinib in patients with uncontrolled blood pressure. Optimize blood pressure prior to initiating selpercatinib treatment. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertension therapy as appropriate. Withhold, reduce

dose, or permanently discontinue Retsevmo based on the severity (see “posology and administration”).

QT Interval Prolongation

QT interval prolongation was reported in patients receiving selpercatinib in clinical trials (see “Properties/Effects”). There were no reports of *torsades de pointes*, events of Grade ≥3 or clinically significant treatment-emergent arrhythmias, ventricular tachycardia, ventricular fibrillation, or ventricular flutter. Fatal events of sudden death and cardiac arrest were reported in patients with significant cardiac history. Selpercatinib should be used with caution in patients with such conditions as congenital long QT syndrome or acquired long QT syndrome or other clinical conditions that predispose to arrhythmias.

Clinical trials with selpercatinib excluded patients with QTc interval > 470 ms at baseline, clinically significant active cardiovascular disease or recent myocardial infarction.

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure.

Monitor electrocardiograms, electrolytes and TSH in all patients at baseline, after 1 week of selpercatinib treatment, at least monthly for the first 6 months of selpercatinib treatment, and every 3 months afterwards, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating selpercatinib and during treatment. Referral to a specialist should occur when clinically indicated and/or for QTc prolongation events that are ≥ Grade 3.

Concomitant use of other drugs known to prolong QTc interval should be avoided.

Monitor the QT interval more frequently when selpercatinib is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withold and dose reduce or permanently discontinue selpercatinib based on severity (see “posology and administration”).

Hypothyroidism

Hypothyroidism was reported in patients receiving selpercatinib in clinical trials (see Undesirable Effects). All patients should be observed closely for signs and symptoms of thyroid dysfunction during selpercatinib treatment. Thyroid function should be monitored before and periodically throughout treatment with selpercatinib. Patients who develop thyroid dysfunction should be treated as medically appropriate, however patients could have an insufficient response to substitution with levothyroxine (T4) as selpercatinib may inhibit the conversion of levothyroxine to triiodothyronine (T3) and supplementation with liothyronine may be needed.

Hemorrhagic Events

Serious including fatal hemorrhagic events can occur with selpercatinib. Permanently discontinue selpercatinib in patients with severe or life-threatening hemorrhage (see “posology and administration”).

Hypersensitivity
Hypersensitivity occurred in patients receiving selpercatinib with a majority of events observed in patients with NSCLC previously treated with anti-PD-1/PD-L1 immunotherapy. Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis.

If hypersensitivity occurs, withhold Retsevmo and begin a treatment with corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume selpercatinib at a reduced dose and increase the dose of selpercatinib by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity (see “posology and administration”). Continue steroids until patient reaches target dose and then tamper. Permanently discontinue selpercatinib for recurrent hypersensitivity.

Risk of Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, selpercatinib has the potential to adversely affect wound healing.

Withhold selpercatinib for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of selpercatinib after resolution of wound healing complications has not been established.

Paediatric population
Data in the paediatric population is limited.

Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis in Adolescent Patients
Slipped Capital Femoral Epiphysis/ Slipped Upper Femoral Epiphysis (SCFE/SUFE) has been reported in adolescent patients receiving selpercatinib (see “*Undesirable Effects*”). Monitor patients for symptoms indicative of SCFE/SUFE and treat as medically and surgically appropriate.

Contraception in females and males
Women of childbearing potential must use highly effective contraception during treatment and for at least two weeks after the last dose of selpercatinib. Men with female partners of childbearing potential should use effective contraception during treatment and for at least two weeks after the last dose of selpercatinib.

Fertility

Based on nonclinical safety findings, male and female fertility may be compromised by treatment with Retsevmo (see "*Preclinical data"*). Both men and women should seek advice on fertility preservation before treatment.

Concomitant oncogenic driver mutations

The efficacy and safety of selpercatinib in patients with known oncogenic driver alterations has not been established. The following driver mutations have been excluded from Libretto-001 study:

- NSCLC: EGFR or MET mutations, ALK or ROS rearrangements, activating mutation KRAS
- MTC: ALK or RAS rearrangements
- Thyroid carcinoma (except MTC): BRAF mutation or activating RAS mutation.

Interactions

Effect of selpercatinib on other medicinal products

Sensitive CYP2C8 substrates

Coadministration of selpercatinib with sensitive CYP2C8 substrates may increase plasma concentrations of the CYP2C8 substrates, this can result in an increase in adverse drug reactions, when already small increases in CYP2C8 substrate concentrations can result in an increase in adverse drug reactions. If the concomitant use cannot be avoided, the medicinal product information of the concomitantly administered medicinal product should be considered for possible dose adjustments.

Selpercatinib increased the C_{max} and AUC of repaglinide (a substrate of CYP2C8) by approximately 188% and 91% respectively. Therefore, coadministration with sensitive CYP2C8 substrates (e.g., enzalutamide, paclitaxel, repaglinide, torasemide, sorafenib, buprenorphine, selexipag, dasabuvir and montelukast), should be avoided.

Sensitive CYP3A4 substrates

Coadministration of selpercatinib with sensitive CYP3A4 substrates may increase plasma concentrations of the CYP3A4 substrates, this can result in an increase in adverse drug reactions., when already small increases in CYP3A4 substrate concentrations can result in an increase in adverse drug reactions. If the concomitant use cannot be avoided, the medicinal product information of the concomitantly administered medicinal product should be considered for possible dose adjustments.

Selpercatinib increased C_{max} and AUC of midazolam (a CYP3A4 substrate) by approximately 39% and 54%, respectively. Therefore, concomitant use with sensitive CYP3A4 substrates, (e.g.,

alfentanil, avanafil, darifenacin, darunavir, midazolam, naloxegol, simvastatin, tipranavir, triazolam, vardenafil), should be avoided.

Effect of other medicinal products on selpercatinib

Sepercatinib metabolism is through CYP3A4. Therefore, medicinal products that can influence CYP3A4 enzyme activity may alter the pharmacokinetics of selpercatinib.

Strong CYP3A4 inhibitors
Agents that may increase selpercatinib plasma concentrations
Selpercatinib is metabolized predominantly by CYP3A4. Coadministration of selpercatinib with a strong CYP3A4 inhibitor may increase selpercatinib plasma concentrations (see "Dosage/Administration").
Itraconazole increased the C_{max} and AUC of selpercatinib by 30% and 130%, respectively, compared to selpercatinib given alone. If strong CYP3A and/or P-gp inhibitors, including, but not limited to, ketoconazole itraconazole, voriconazole, ritonavir, saquinavir, and posaconazole, have to be co-administered, the dose of selpercatinib should be reduced (see «*Dosage/Administration*»).

Strong CYP3A4 inducers

Agents that may decrease selpercatinib plasma concentrations

Coadministration of selpercatinib with a strong CYP3A4 inducer may decrease selpercatinib plasma concentrations (see «Dosage/Administration»).
Coadministration of rifampicin, a strong CYP3A4 inducer resulted in a decrease of approximately etwa 87% and 70% in selpercatinib C_{max} and AUC respectively, compared to selpercatinib alone, therefore the concomitant use of strong CYP3A4 inducers including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (Hypericum perforatum), should be avoided.

Other interactions

Coadministration with medicinal products that affect gastric pH
Selpercatinib has pH-dependent solubility, with decreased solubility at higher pH that can result in a loss of efficacy (see "Dosage/Administration").

No clinically significant differences in selpercatinib pharmacokinetics were observed when coadministered with multiple daily doses of ranitidine (H_2 receptor antagonist) given 2 hours after the selpercatinib dose.

Coadministration with medicinal products that are proton pump inhibitors

Coadministration with multiple daily doses of omeprazole (a proton pump inhibitor) decreased selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when selpercatinib was administered fasting. Coadministration with multiple daily doses of omeprazole did not significantly change the selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when Retsevmo was administered with food.
Under fasting conditions, coadministration of omeprazole led to a 69% to 88% lower overall and peak exposure to selpercatinib compared to selpercatinib administered alone.

Coadministration with medicinal products that are substrates of transporters
Selpercatinib inhibits the renal transporter multidrug and toxin extrusion protein 1 (MATE1). In vivo interactions of selpercatinib with clinically relevant substrates of MATE1, such as creatinine, may occur.
Selpercatinib is an in vitro inhibitor of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).
In vivo, selpercatinib increased Cmax and AUC of dabigatran, a P-gp substrate, by 43% and 38%, respectively. Therefore, caution should be used when taking a sensitive P-gp substrate (e.g., fexofenadine, dabigatran etexilate, colchicine, saxagliptin), and particularly those with a narrow therapeutic index (e.g., digoxin) (see section "*Pharmacokinetic* ").

Selpercatinib is an in vitro substrate for P-gp and BCRP.
Selpercatinib is a substrate for P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) *in vitro*, however these transporters do not appear to limit the oral absorption of selpercatinib, as its oral bioavailability is 73% and its exposure was increased minimally by co-administration of the P-gp inhibitor rifampicin (increase of approximately 6.5% and 19% in selpercatinib $AUC_{0\text{-}24}$ and C_{max}, respectively).

Paediatric population
Interaction studies have only been performed in adults.

In vitro Data
CYP enzymes: Selpercatinib is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant selpercatinib concentrations.

Transporter systems: Selpercatinib is an inhibitor of MATE1, P-gp, and BCRP, but not of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, and MATE2-K at clinically relevant Selpercatinib concentrations. Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1. Selpercatinib is a substrate of P-gp and BCRP, but not of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K.

Pregnancy, lactation

Contraception

Women of childbearing potential have to use a reliable contraception during treatment and for at least 2 weeks after the last dose of selpercatinib. Men with female partners of childbearing potential should use a reliable contraception during treatment and for at least 2 weeks after the last dose of selpercatinib.

Pregnancy

There are no available data from the use of selpercatinib in pregnant women. Studies in animals have shown reproductive toxicity (see “Preclinical data”). It should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus. Pregnant women should be informed about the risk to the foetus.

Lactation

It is unknown whether selpercatinib is excreted in human milk. A risk to newborns/infants cannot be excluded. Due to the potential risk for the breastfed child, breastfeeding should be discontinued during treatment with Retsevmo and for at least 2 weeks after the last dose.

Fertility

The effect of Selpercatinib on human fertility is unknown. Based on results from nonclinical safety studies, Retsevmo may compromise male and female fertility (see «Preclinical data».

Effects on ability to drive and use machines

No studies have been conducted to determine the effects of selpercatinib on the ability to drive or use machines. In the absence of studies to determine the ability to drive and use machines while receiving selpercatinib patients should be advised to be cautious when driving or using machines in case they experience fatigue or dizziness during treatment with Retsevmo (see "Undesirable effects").

Undesirable effects

Summary of the safety profile

Unless otherwise described the integrated frequency of ADRs reported in patients treated with selpercatinib from two open-label multicentre, dose-escalation phase 1/2 studies (LIBRETTO-001 and LIBRETTO-121), and from two open-label, multicentre randomised phase 3 comparative studies (LIBRETTO-431 and LIBRETTO-531) are summarised.
The most common adverse reactions (>20%) observed in selpercatinib-treated patients are oedema, diarrhoea, fatigue, hypertension, dry mouth, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, rash, abdominal pain, constipation, nausea, creatinine increased, headache, vomiting, haemorrhage and decreased appetite.
The most common serious adverse drug reactions (ADRs) (≥ 1.0%) serious adverse drug reactions (ADRs) are pneumonia (6.0%), haemorrhage (2.9%), abdominal pain (2.3%), blood sodium decreased (2.1%), diarrhoea (1.6%), vomiting (1.6%), pyrexia (1.5%), blood creatinine increased (1.5%), hypersensitivity (1.4%), urinary tract infections (1.4%), nausea (1.2%), ALT increased (1.0.%), AST increased (1.0%) and fatigue (1.0%).
Permanent discontinuation of Retsevmo for treatment emergent adverse events, regardless of attribution occurred in 9 %of patients.
The most common ADRs resulting in permanent discontinuation (3 or more patients) were increased ALT (0.6%), fatigue (0.5%), increased AST (0.4%), pneumonia (0.3%), blood bilirubin increased (0.3%), electrocardiogram QT prolonged (0.2%), haemorrhage (0.2%), hypersensitivity (0.2%), platelet count decreased (0.2%).

The adverse drug reactions [b] reported in the 1241 patients treated with Retsevmo in Study LIBRETTO-001, Study LIBRETTO-121, Study LIBRETTO-431, and Study LIBRETTO-531 are described below.

The adverse drug reactions are classified according to the MedRASystem Organ Class.
Frequency groups are defined by the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), and not known (cannot be estimated from available data).

Infections and infestations
Very common: Urinary tract infections[a] (17.7%, Grade ≥ 3: 2.1%), Pneumonia[b] (11.8 %, Grade ≥ 3: 6.3%).

Immune system disorders[c]

Common: Hypersensitivity[d]

Endocrine disorders

Very common: Hypothyroidsm (15.6%)

Metabolism and nutrition disorders

Very Common: Decreased appetite (20.4%, Grade ≥ 3: 0.7%), Magnesium decreased[t] (11.8%, Grade ≥ 3: 0.3%), Calcium decreased (16.3 %, Grade≥ 3: 2.5%), albumin decreased (15.1%, Grade ≥ 3: 0.9%), Sodium decreased (14.7%, Grade ≥ 3 6.9%), Potassium decreased (11.0%, Grade ≥ 3 2.2%) .
uncommon: Tumour Lysis syndrome.

Nervous system disorders

Very common: Headache[e] (26.5%, Grade ≥ 3: 1.3%), Dizziness[f] (18.2%, Grade ≥3: 0.4%)

Cardiac disorders

Very common: Electrocardiogram QT prolonged[g] 19.7%, Grade ≥ 3: 5.6%,)

Vascular disorders

Very common: Hypertension[h] (43.3%, Grade ≥3: 20.0%), Haemorrhage[i](23.0%, Grade ≥ 3: 3.2%).

Respiratory, thoracic and mediastinal disorders

Common: Chylothorax, Intestitial lung disease/ pnenomitis[J]

Gastrointestinal disorders

Very common: Diarrhoea[k] (46.7%, Grade ≥3: 4.9%), Dry Mouth[l] (40.9% Grade ≥3: 0.1%), Abdominal pain[m] (33.4%, Grade≥ 3: 2.4%), Constipation (30.6%, Grade ≥3: 0.9%), Nausea (29.3%, Grade≥ 3: 1.6%), Vomiting[n] (23.4%, Grade ≥ 3: 2.2%), stomatitis[o] (16.7%, Grade≥ 3: 0.3%).
Common: Chylous ascites[p]

Skin and subcutaneous tissue disorders

Very common: Rash[q] (34.7%, Grade≥ 3: 1.1%)

Musculoskeletal and connective tissue disorders

Common: Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis has been observed (6.4%) in pediatric and adolescent patients treated with selpercatinib (n=47).

Reproductive system and breast disorders

Erectile dysfunction has been very commonly observed (21.4%) in male patients with RET-mutant medullary thyroid cancer treated with selpercatinib across clinical trials LIBRETTO-001 and LIBRETTO-531 (n=336).

General disorders and administration site conditions

Very common: Oedema[r](47.9%, Grade≥ 3: 1.2%), Fatigue[s] (44.0%, Grade≥ 3: 4.0%), Pyrexia (18.4%, Grade≥ 3: 0.5%).

Hepatobiliary disorders[t]

Very common: ALT Increased (38.3%, Grade ≥ 3: 12.9%), AST Increased (39.4%, Grade≥ 3: 8.7%), total bilirubin increased (17.9%, Grade ≥ 3: 1.6%), Alkaline phosphatase increased (14.6%, Grade≥ 3: 2.1%).

Renal disorders[t]

Very common: Creatinine increased (27.5%, Grade ≥3: 2.3%)

Blood and Lymphatic disorders[t]

Very common lymphocyte count decreased (12.1%, Grade≥ 3: 4.9%), platelets decreased (16.8%, Grade≥ 3: 2.9%), haemoglobin decreased (14.7%, Grade≥ 3: 2.9%), neutrophil count decreased (13.1%, Grade≥ 3: 2.4%, white blood cell count decreased (16.3%, Grade≥ 3: 1.4%).

[a] Urinary tract infections includes urinary tract infection, cystitis, urosepsis, escherichia urinary tract infection, escherichia pyelonephritis, kidney infection, nitrite urine present, pyelonephritis, urethritis, urinary tract infection bacterial and urogenital infection fungal.

[b] Pneumonia includes pneumonia, lung infection, pneumonia aspiration, empyema, lung consolidation, pleural infection, pneumonia bacterial, pneumonia staphylococcal, atypical pneumonia, lung abscess, pneumocystis jirovecii pneumonia, pneumonia pneumococcal, pneumonia respiratory syncytial viral, infectious pleural effusion, and pneumonia viral.

[c] Hypersensitivity reactions were characterised by a maculopapular rash often preceded by a fever with associated arthralgias/myalgias during the patient's first cycle of treatment (typically between Days 7-21).

[d] Hypersensitivity includes drug hypersensitivity and hypersensitivity.

[e] Headache includes headache, sinus headache and tension headache.

[f] Dizziness includes dizziness, vertigo, presyncope and dizziness postural.

[g] Electrocardiogram QT prolonged includes electrocardiogram QT prolonged and Electrocardiogram QT interval abnormal.

[h] Hypertension includes hypertension and blood pressure increased.

[i] Haemorrhage includes epistaxis, haemoptysis, contusion, haematuria, rectal haemorrhage, vaginal haemorrhage, cerebral haemorrhage, traumatic haematoma, blood urine present, conjunctival haemorrhage, ecchymosis, gingival bleeding, haematochezia, petechiae, blood blister, spontaneous haematoma, abdominal wall haematoma, anal haemorrhage, angina bullosa haemorrhagica, disseminated intravascular coagulation, eye haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haemorrhage intracranial, haemorrhage subcutaneous, haemorrhoidal haemorrhage, hepatic haematoma, intra-abdominal haemorrhage, mouth haemorrhage, oesophageal haemorrhage, pelvic haematoma, periorbital haematoma, periorbital haemorrhage, pharyngeal haemorrhage, pulmonary contusion, purpura, retroperitoneal haematoma, skin haemorrhage, subarachnoid haemorrhage, diverticulum intestinal haemorrhagic, eye haematoma, haematemesis, haemorrhage, haemorrhagic stroke, hepatic haemorrhage, laryngeal haemorrhage, lower gastrointestinal haemorrhage, melaena, menorrhagia, occult blood positive, post procedural haemorrhage, postmenopausal haemorrhage, retinal haemorrhage, scleral haemorrhage, subdural haemorrhage, traumatic haemothorax, tumour haemorrhage, upper gastrointestinal haemorrhage, uterine haemorrhage and vessel puncture site haematoma,haemarthrosis,haematoma, arterial haemorrhage, eye contusion, haemothorax, subdural haematoma, testicular haemorrhage, tracheal haemorrhage, international normalized ratio increased, activated partial thromboplastin time prolonged, occult blood positive, coagulopathy, haemoglobin decreased, fibrin D dimer increased, and red blood cell count decreased.

[j] Interstitial lung disease/pneumonitis includes interstitial lung disease, pneumonitis, radiation pneumonitis, restrictive pulmonary disease, acute respiratory distress syndrome, alveolitis, bronchiolitis, langerhans' cell histiocytosis, pulmonary radiation injury, cystic lung disease, lung infiltration and lung opacity.

[k] Diarrhoea includes diarrhoea, anal incontinence, defaecation urgency, frequent bowel movements and gastrointestinal hypermotility.

[l] Dry mouth includes dry mouth and mucosal dryness.

[m] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower and gastrointestinal pain.

[n] Vomiting includes vomiting, retching and regurgitation.

[o] Stomatitis includes stomatitis, mouth ulceration, mucosal inflammation and oral mucosal blistering.

[p] Chylous ascites includes chylous ascites and ascites chylous (MedDRA LLTs).

[q] Rash includes rash, rash maculo-papular, dermatitis, skin exfoliation, rash macular, rash erythematous, urticaria, dermatitis allergic, exfoliative rash, rash papular, rash morbilliform, rash pruritic, rash vesicular, butterfly rash, rash follicular, rash generalised, rash pustular and skin reaction.

[r] Oedema includes oedema peripheral, face oedema, periorbital oedema, swelling face, localised oedema, peripheral swelling, generalised oedema, eyelid oedema, eye swelling, lymphoedema, oedema genital, scrotal swelling, angioedema, eye oedema, oedema, scrotal oedema, skin oedema, swelling, orbital oedema, testicular swelling, vulvovaginal swelling, orbital swelling, penile odemea, periorbital swelling and swelling of eyelid.

[s] Fatigue includes fatigue, asthenia and malaise.

[t] Based on laboratory assessments. Percentage is calculated based on the number of patients with baseline assessment and at least one post-baseline assessment as the denominator.

Description of selected undesirable effects

Transaminase elevations (AST / ALT increased)

Across all studies (as of May 2024), based on laboratory assessment, ALT and AST elevations were reported in 38.3% and 39.4% patients, respectively. Grade 3 or 4 ALT or AST elevations were reported in 12.9% and 8.7% patients respectively. ALT was reported in 1% of patients as serious and AST was reported in 1% of patient as serious.

The median time to first onset was: AST increase 4.7 weeks (range: 0.7, 227.9), ALT increase 4.4 weeks (range: 0.9, 186.1) in LIBRETTO-001 (as of January 2023), AST increase 5.1 weeks (range: 0.7, 88.1), ALT increase 5.1 weeks (range: 0.7, 110.9) in LIBRETTO-431 (as of May 2023), AST increase 6.1 weeks (range: 0.1, 85.1), ALT increase 6.1 weeks (range: 0.1, 85.1) in LIBRETTO-531 (as of May 2023).

Dose modification is recommended for patients who develop Grade 3 or 4 ALT or AST increase (see "*Dosage/Administration*").

QT interval prolongation

In the 837 patients in study LIBRETTO-001 as of January 2023 who had ECGs, review of data showed 8.1% of patients had >500 msec maximum post-baseline QTcF value, and 21.6% of patients had a >60 msec maximun increase from baseline in QTcF intervals. In the 156 patients in LIBRETTO-431 as of May 2023 who had ECGs, 5.1% of patients had >500 msec maximum post-baseline QTcF value, and 16.7% of patients had a >60 msec maximum increase from baseline in QTcF intervals. In the 191

patients in LIBRETTO-531 as of May 2023 who had ECGs, 3.7% of patients had >500 msec maximum post-baseline QTcF value, and 17.8% of patients had a >60 msec maximum increase from baseline in QTcF intervals.

Across all studies (as of May 2024), in LIBRETTO-001, LIBRETTO-431, LIBRETTO-531 and LIBRETTO-121 studies, there were no reports of *torsades de pointes*, events of Grade ≥3 or clinically significant treatment-emergent arrhythmias, ventricular tachycardia, ventricular fibrillation, or ventricular flutter. Fatal events of sudden death and cardiac arrest were reported in patients with significant cardiac history. Across all studies, two patients (0.2%) discontinued selpercatinib treatment due to QT prolongation.
Retsevmo may require dose interruption or modification (see “Dosage/Administration” and “Warnings and precautions”).

Hypertension
Across all studies (as of May 2024), hypertension has been reported in 43.3% of patients, grade ≥3 in 20.0% of patients.

In the 837 patients of the study LIBRETTO-001 as of January 2023 who had blood pressure measurement, the median maximum increase from baseline systolic pressure was 32 mm Hg (range: -15, +100). Diastolic blood pressure results were similar, but the increases were of lesser magnitude. In LIBRETTO-001, only 10.3% of patients retained their baseline grade during treatment, 40.7% had an increasing shift of 1 grade, 38.5% of 2 grades, and 9.8% of 3 grades.

Overall, a total of 19.68% in LIBRETTO-001, 20.3% in LIBRETTO-431 (May 2023), and 19.2% in LIBRETTO-531 (May 2023) displayed treatment-emergent Grade 3 hypertension (defined as maximum systolic blood pressure greater than 160 mm Hg). Grade 4 treatment emergent hypertension was reported in 0.1% of patients in LIBRETTO-001 (January 2023), and no reports in LIBRETTO-431 and LIBRETTO-531 (both May 2023).
Two patients (0.2%) permanently discontinued treatment due to hypertension in LIBRETTO-001 (January 2023), and no patients in LIBRETTO-431 and LIBRETTO-531 (both May 2023).
Dose modification is recommended in patients who develop hypertension (see “*Dosage/Administration*”). Selpercatinib should be suspended temporarily for medically significant hypertension until controlled with antihypertensive therapy. Dosing should be resumed at the next lower dose if clinically indicated.

Increased Creatinine

In healthy subjects administered selpercatinib 160 mg orally twice daily, serum creatinine

increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed *(see Properties/Effects).*

Additional information on special populations

Paediatric population

There were 3 patients < 18 years (range 15-17) of age with RET-mutant MTC in LIBRETTO-001. There were 11 patients < 18 years (range 6-17) of age with RET fusion-positive thyroid cancer and 12 patients < 18 years (range 2-17) of age with RET-mutant MTC in LIBRETTO-121. There was 1 patient 12 years of age with RET-mutant MTC in LIBRETTO-531.

Of the total 33 patients in LIBRETTO-121, 97% of patients reported treatment-emergent adverse events. The most common AEs (≥25%) were diarrhoea, pyrexia, nausea, abdominal pain, headache, AST increased, ALT increased, coronavirus infection, cough, epistaxis, and vomiting.

Grade ≥3 treatment-emergent AEs occurred in 57.6% of patients. The most common Grade ≥3 AEs were weight increased (12.1%), vomiting (9.1%), ALT increased (6.1%), constipation (6.1%), hypokalaemia (6.1%), and neutrophil count decreased (6.1%).
Serious adverse events occurred in 42.4% of patients. The most frequent serious adverse event was vomiting (6.1%). All other SAEs were reported in 1 patient each. No fatal events were reported.

Animal Toxicity Data indicate a potential risk of growth disorders in children who have not reached final body height (see preclinical data).
Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis (SCFE/SUFE) has been reported in 3 paediatric patients receiving selpercatinib in clinical studies (*see "Warnings and precautions"*)

Elderly

In patients receiving selpercatinib, 24.7% were ≥65-74 years of age, 8.6% were 75-84 years of age, and 1.0% ≥ 85 years of age in study LIBRETTO-001. The safety profile in elderly patients (≥ 65 years) is consistent with that seen in younger patients (< 65 years).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Symptoms of overdose have not been established. In the event of suspected overdose, supportive care should be provided.

Properties/Effects

ATC code

L01EX22

Mechanism of action

Selpercatinib is a small molecule inhibitor of the rearranged during transfection (*RET*) receptor tyrosine kinase. Selpercatinib inhibited wild type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3 with IC50 values ranging from 0.92 nM to 67.8 nM. In other enzyme assays, selpercatinib also inhibited FGFR 1, 2, and 3 at higher concentrations that were still clinically achievable. Selpercatinib was 250 times more selective for RET than for 98% of ~300 kinases, including VEGFR2, tested in preclinical studies. In cellular assays, selpercatinib inhibited RET at approximately 60 fold lower concentrations than FGFR1 and 2 and approximately 8 fold lower concentration than VEGFR3.
Certain point mutations in RET or chromosomal rearrangements involving in frame fusions of RET with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers by promoting cell proliferation of tumor cell lines. In in vitro and in vivo tumor models, selpercatinib demonstrated anti tumor activity in cells harboring constitutive activation of RET protein resulting from gene fusions and mutations, including CCDC6 RET, KIF5B RET, RET V804M, and RET M918T. In addition, selpercatinib showed anti-tumor activity in mice intracranially implanted with a patient-derived RET fusion positive tumor.

Pharmacodynamics

Cardiac Electrophysiology
In a thorough QT study with positive control in 32 healthy subjects an exposure-response analysis indicated that supra therapeutic concentrations, could lead to an increase in QTc > 20 ms.
In patients receiving selpercatinib, QT interval prolongation was reported. Therefore, dose interruption or modification may be required in patients (*see “posology and warning and precations”).*

Clinical efficacy

The efficacy of Retsevmo was evaluated in adult patients with advanced RET fusion-positive NSCLC, RET-mutant MTC and RET fusion-positive thyroid cancer patients enrolled in a phase 1/2, multicenter, open-label, single-arm clinical trial: Study LIBRETTO-001.
Patients in both the phase 1 and phase 2 portions of the study had progressed on or were intolerant to standard therapy, or no standard therapy existed.
Patients in both the phase 1 and phase 2 portions of the study had progressed on or were intolerant to standard therapy, or no standard therapy existed.
Patients with CNS metastases were eligible if stable, while patients with symptomatic primary CNS tumour, metastases, leptomeningeal carcinomatosis or spinal cord compression were excluded. 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. Patients in the phase 2 portion of the study received Retsevmo 160 mg orally twice daily until unacceptable toxicity or disease progression. Identification of a RET gene alteration was prospectively determined in local laboratories using next-generation sequencing (NGS), polymerase chain reaction (PCR), or fluorescence in situ hybridization (FISH). The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

Treatment-naive RET fusion-positive non-small cell lung cancer

LIBRETTO-431

The efficacy of Retsevmo in RET fusion-positive NSCLC was evaluated in LIBRETTO-431, a phase 3 multicentre, randomised, open-label study, comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with advanced or metastatic RET fusion-positive NSCLC. Adult patients with histologically confirmed, unresectable, locally advanced or metastatic NSCLC with no previous systemic therapy for metastatic disease were eligible. Patients who received adjuvant or neoadjuvant therapy if the last dose of systemic treatment was completed at least 6 months prior to randomisation were also eligible. Patients with a squamous histology, and those with cardiovascular disease, history of myocardial infarction within 6 months, QTc interval of > 470 ms, or were taking a medication known to cause QTc prolongation were excluded. Patients received 160 mg of selpercatinib twice daily (starting dose) or platinum-based and pemetrexed therapy with or without pembrolizumab. Identification of a RET gene alteration was prospectively determined using next generation sequencing (NGS) or polymerase chain reaction (PCR). Patients were stratified according to geographic region (East Asia vs. elsewhere), status with respect to investigator assessed brain metastases at baseline (absent or unknown vs present), and whether the

investigator had intended (before randomisation) to treat the patient with or without pembrolizumab. The primary efficacy outcome measure was PFS per RECIST 1.1 by BICR sequentially assessed first in the population of patients with the investigator intent to receive pembrolizumab (ITT-pembrolizumab) if randomized to control and then in the overall intention to treat (ITT) population. Error controlled secondary efficacy outcomes included OS.

The median age of patients in the ITT population was 62.5 years (range 31 to 87 years). 54.8% of patients were female. 40.2% of patients were White, 57.4% were Asian, 0.8% were Black. 67.4% were never smokers. In the ITT population, 93.5% had metastatic disease, and 19.5% of patients had CNS metastases at baseline. ECOG performance status was reported as 0-1 (96.9%) or 2 (3.1%). The most common fusion partner was KIF5B (46.0%), followed by CCDC6 (9.6%).

Of the 261 patients enrolled and randomized in Study LIBRETTO-431 ITT population, 212 were stratified to form the ITT-Pembrolizumab population. In the ITT-Pembrolizumab population, 129 patients received selpercatinib while 83 received platinum-based pemetrexed chemotherapy with pembrolizumab.

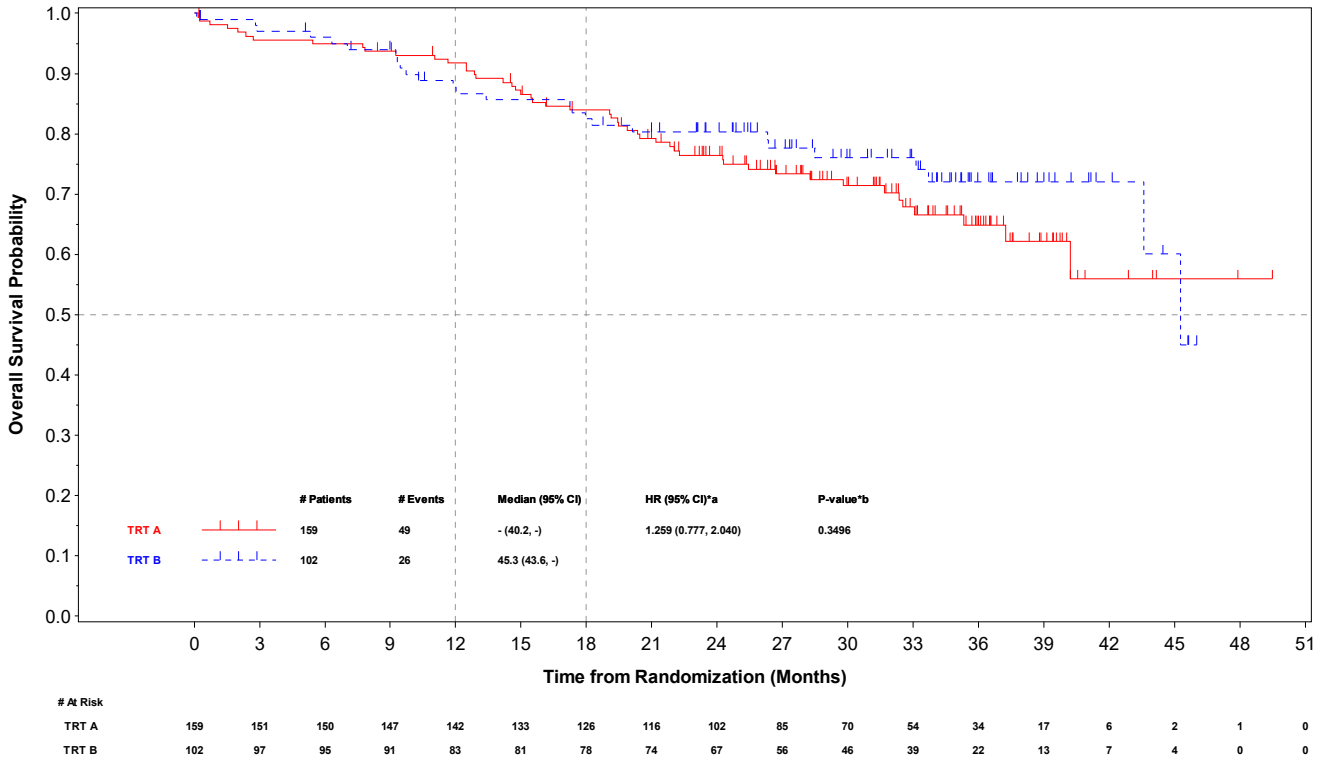
The median age of patients in the ITT-Pembrolizumab population was 61.5 years (range 31 to 84 years). 53.3% of patients were female. 41.3% of patients were White, 56.3% were Asian, 1% were Black. 67.9% were never smokers. In the ITT Pembrolizumab population, 93% had metastatic disease, and 20.3% of patients had CNS metastases at baseline. ECOG performance status was reported as 0-1 (96.7%) or 2 (3.3%). The most common fusion partner was KIF5B (44.8%), followed by CCDC6 (9.9%). The study met its primary endpoints of improving PFS in both the ITT-Pembrolizumab and ITT populations.

At the time of a preplanned interim efficacy analysis (01 May 2023), in the ITT population, the median progression-free survival was 24.84 months (95% confidence interval [CI]: 17.31, NE) with selpercatinib arm and 11.17 months (95% CI: 8.77, 16.76) in the control arm with hazard ratio (HR) for progression or death, 0.482 (95% CI: 0.331, 0.700; p=.0001).

At the time of a preplanned interim efficacy analysis (1 May 2023), in the ITT-Pembrolizumab population the median progression-free survival was 24.84 months (95% confidence interval [CI], 16.89 to not estimable) with selpercatinib and 11.17 months (95% CI, 8.77 to 16.76) with control treatment (hazard ratio for progression or death, 0.465; 95% CI, 0.309 to 0.699; P = 0.0002).

OS was not mature at the time of the primary PFS analysis. At the time of an updated descriptive interim analysis of OS (1 May 2024) (43% of prespecified OS events needed for the final analysis), in the ITT population, 75 events were observed across the two arms (49 (31% in the ITT) in the selpercatinib arm and 26 (25%) in the control arm and the HR was 1.259 ([95% CI: 0.777, 2.040];

Figure 1. LIBRETTO-431: Kaplan-Meier plot of OS (BICR assessment, ITT population)



Abbreviations: CI = confidence interval; HR = hazard ratio; TRT A = Selpercatinib; TRT B = Carboplatin or Cisplatin+Pemetrexed+/-Pembrolizumab.
*a HR - IWRS stratified hazard ratio from Cox proportional hazard model and 95% CI of TRT A versus TRT B.
*b Log-rank IWRS stratified p-value(2-sided) for comparison of TRT A versus TRT B

Data Cut-off date: 01 May 2024

Of 68 control arm patients who had disease progression, 50 patients (74%) received selpercatinib at progression. Of 71 selpercatinib arm patients who had disease progression, 16 (23%) received chemotherapy and/or immune checkpoint inhibitor therapy, and 44 (62%) continued receiving selpercatinib.

Previously treated RET fusion-positive Non-Small Cell Lung Cancer

A total of 247 patients in LIBRETTO-001 had received prior platinum based chemotherapy. The median age was 61 years (range 23 years to 81 years). 56.7% of patients were female. 43.7% of patients were White, 47.8% were Asian, 4.9% were Black, and 66.8% were never smokers. Most patients (98.8%) had metastatic disease at enrolment and 31.2% had CNS metastasis at baseline as assessed by investigator. ECOG performance status was reported as 01 (97.1%) or 2 (2.8%). The most common fusion partner was KIF5B (61.9%), followed by CCDC6 (21.5%) and then NCOA4 (2.0%). Two patients had locally advanced NSCLC and 1 patient had squamous cell NSCLC. The median number of prior systemic therapies was 2 (range 1–15) and 43.3% (n = 107/247) received 3 or more prior systemic regimens; prior treatments included anti PD1/PDL1 therapy (58.3%), multikinase inhibitor (MKI) (31.6%) and taxanes (34.8%); 41.3% had other systemic therapy.

As of data cut-off date 13 January 2023, in the efficacy eligible patient population (patients who had received prior platinum based chemotherapy and with at least 6 months follow up on LIBRETTO-001, n= 247) , the objective response rate (ORR) was 61.5% (95% CI: 55.2-67.6) and the median duration of response was 31.6 months (95% CI: 20.4-42.3) with a median follow-up of 39.52 months.

Vandetanib and cabozantinib naïve RET-mutant medullary thyroid cancer

LIBRETTO-531

The efficacy of Retsevmo in *RET*-mutant MTC was evaluated, in LIBRETTO-531, a phase 3 multicenter, randomised, open-label comparator study, comparing selpercatinib to physician's choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC. Adult or adolescent patients with histologically confirmed, unresectable, locally advanced, or metastatic MTC with no previous treatment with a kinase inhibitor were eligible.

Patients were required to have radiologic progressive disease per RECIST 1.1 at screening compared with an image obtained within the prior 14 months and those with cardiovascular disease, history of myocardial infarction within 6 months, QTc interval of > 470 ms, or were taking a medication known to cause QTc prolongation were excluded. Patients received 160 mg of selpercatinib twice daily (starting dose) or physician's choice of cabozantinib (140 mg once daily) or vandetanib (300 mg once daily). Identification of a RET gene alteration was prospectively determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR). Patients were stratified according to *RET* mutation (M918T vs. other), and the intended treatment if randomised to control arm

(cabozantinib vs vandetanib). The primary efficacy outcome measure was PFS per RECIST 1.1 by BICR. Key secondary efficacy outcomes included treatment failure-free-survival (TFFS) and comparative tolerability. Other secondary efficacy outcomes included OS.

Of the 291 patients enrolled and randomised in LIBRETTO-531 to form the ITT population, 193 were randomised to the selpercatinib arm, and 98 were randomised to the control arm. Of the 98 patients randomised to the control arm, 73 were stratified to cabozantinib, and 25 were stratified to vandetanib. The median age of patients in the ITT population was 55 years (range: 12 to 84 years). 37.1% of patients were female. 69.4% of patients were White, 27.7% were Asian, 2.9% were Black. Most patients (77%) had metastatic disease at enrolment. 8.2% of patients had M0 stage (i.e. no distant metastasis at time of study enrollment).
ECOG performance status was reported as 0-1 (98.3%) or 2 (1%). The most common mutation was M918T-(62.5%).
The study met its primary endpoint of improving PFS in the ITT population (data cut off 22 May 2023).

At a median follow-up of 12 months, median progression-free survival as assessed by blinded independent central review was not reached in the selpercatinib group and was 16.8 months (95% confidence interval [CI], 12.22 to 25.10) in the control group (hazard ratio for disease progression or death, 0.280; 95% CI, 0.165 to 0.475; P<0.0001)

Median duration of treatment failure-free survival (TFFS) was not reached with selpercatinib, and was 13.9 months in the control group (27 events in selpercatinib arm, versus 37 events in control arm,HR 0.254; 95% CI: 0.153, 0.423; p<0.0001).

At a later OS analysis, with a data lock of 11 March 2024, 26 events were observed across the two arms and the HR was 0.275 (95% CI: 0.124, 0.608). The PFS HR for this analysis was 0.202 (95% CI: 0.128, 0.320) and the ORR for selpercatinib was 82.4% compared to 43.9% for the control arm.

Efficacy in paediatric patients
The evidence for the efficacy and the safety of selpercatinib in the adolescent population is limited. Only 1 patient under 18 years with treatment naïve RET mutant MTC was included in study LIBRETTO-531, and there are in total results from 3 patients under 18 years from study LIBRETTO-001, 2 of them with treatment naïve RET mutant MTC. Further results from a total of 14 pediatric patients with RET Mutant MTC and a total of 10 pediatric patients with RET fusion-positive thyroid cancer from the Phase 1/2 Study LIBRETTO-121 are presented. The ORR assessed by IRC in LIBRETTO-121 was 42.9% (95% CI 17.7, 71.1%) in the RET-mutant MTC population (n=14) and 60% (95% CI 26.2, 87.8) in the RET fusion-positive thyroid cancer population (n=10), this compares to the ORR in adults which was 77.5% in RET-mutant MTC patients (n=117) and 89.2% in RET fusion-positive thyroid cancer patients (n=58).

Previously treated RET fusion-positive thyroid cancer-

Of the *RET* fusion-positive thyroid cancer patients previously treated with systemic therapy other than radioactive iodine, and enrolled in LIBRETTO-001, (data cut-off 13 January 2023), 41 patients had the opportunity to be followed for at least 6 months and were considered efficacy eligible. All 41 patients received prior systemic treatment, and 31 patients also received radioactive iodine treatment.

Within the 41 pretreated patients of the primary analysis set, the following histologies where observed: papillary (n = 31), poorly differentiated (n = 5), anaplastic (n = 4), and Hurthle cell (n = 1).

The median age was 58 years (range 25 to 88 years). 43.9% of patients were male. 58.5% of patients were white while 29.3% were Asian and 7.3% were Black. ECOG performance status was reported as 0-1 (92.7%) or 2 (7.3 %). 100% of patients had metastatic disease.
Patients had received a median of 3 prior systemic therapies (range: 1-7). The most common prior therapies included radioactive iodine (73.2%), MKI (85.4%) and 9.8% had other systemic therapy.

In the primary analysis set with 41 previously treated RET fusion-positive thyroid cancer patients, the objective response rate was 85.4% (95% CI: 70.8, 94.4) and the median duration of response was 26.7 months (95% CI: 12.1-NE) with a median follow-up of 33.87 months.
In the poorly differentiated TC population (n=5), the ORR was 100% (95% CI: 47.82, 100). In the anaplastic TC population (n=4), the ORR was 75% (19.41, 99.37). The single patient with Hurthle cell TC demonstrated a partial response.

Previously treated RET mutant Medullary Thyroid Cancer

Of the RET-mutant MTC patients enrolled in LIBRETTO-001, 152 were previously treated with cabozantinib and/or vandetanib and had the opportunity to be followed for at least 6 months and were considered efficacy eligible., The median age was 58 years (range 17 years to 90 years); 1 patient (0.7%) was <18 years of age. 63.8% of patients were male. 90.1% of patients were white while 1.3% were Asian and 1.3% were Black. ECOG performance status was reported as 0-1 (92.7%) or 2 (7.2%). 98.0% of patients had metastatic disease. 100% (n = 152) of patients received prior systemic therapy with a median of 2 prior systemic regimens and 27.6% (n = 42) received 3 or more prior systemic regimens. The most common mutation was M918T (65.1%), followed by extracellular cysteine mutations (15.8).

In the 152 previously treated RET mutant MTC patients, the objective response rate was 77.6 % (70.2, 84.0) and the median duration of response was 45.3 months (95% CI: 33.6, NE) with a median follow-up of 38.3 months.

Children and adolescents

The evidence for the efficacy and safety of selpercatinib in the adolescent population is limited. Results were presented from a total of 14 pediatric patients with MTC from phase 1/2 study LIBRETTO-121 were presented. LIBRETTO-121 is an ongoing Phase 1/2 study in pediatric patients with an advanced solid or primary CNS tumor who have an activating RET alteration.

The objective response rate (ORR) in the RET-mutated MTC population (n=14) in LIBRETTO-121 was 42.9% (95% CI: 17.7%-71.1%).

Pharmacokinetics

The pharmacokinetics of selpercatinib were evaluated in patients with locally advanced or metastatic solid tumors administered 160 mg twice daily unless otherwise specified. Steady-state selpercatinib AUC and Cmax increased in a dose proportional manner over the dose range of 20 mg once daily to 240 mg twice daily.
Steady-state was reached by approximately 7 days and the median accumulation ratio after administration of 160 mg twice daily was 3.4-fold. Mean steady-state selpercatinib [coefficient of variation (CV%)] Cmax was 2,980 (53%) ng/mL and AUC0 24h was 51,600 (58%) ng*h/mL.

In vitro studies indicate that selpercatinib does not inhibit or induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations.

Absorption

After an oral dose of 160 mg, Retsevmo was rapidly absorbed, with T_{max} of approximately 2 hours. Geometric mean absolute oral bioavailability was 73% (range: 60-82%).

Effect of food

Compared to selpercatinib AUC and C_{max} in the fasted state, selpercatinib AUC was increased by 9% and C_{max} was reduced by 14% after oral administration of a single 160 mg dose to healthy subjects taken with a high-fat meal.

These changes were not considered to be clinically relevant. Therefore, selpercatinib can be taken with or without food.

Distribution

Selpercatinib mean (CV%) volume of distribution (V_{ss}/F) is 191 (69%) L following oral administration of selpercatinib in adult patients. Selpercatinib is 96% bound to human plasma proteins in vitro and it's binding is independent of concentration. The blood-to-plasma concentration ratio is 0.7.

Metabolism

Selpercatinib is metabolized predominantly by CYP3A4. Following oral administration of a single [^{14}C] radiolabeled 160 mg dose of selpercatinib to healthy subjects, unchanged selpercatinib constituted 86% of the measured radioactive components in plasma.

Elimination

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

Kinetics in specific patient groups

Age, gender and body weight

Age (range: 15 years to 90 years) and gender had no clinically meaningful effect on the pharmacokinetics of Retsevmo.

Hepatic impairment

The selpercatinib AUC0-INF increased by 7%, 32%, and 77% in subjects with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST), moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST), and severe (total bilirubin greater than 3 to 10 times ULN and any AST) hepatic impairment, respectively, compared to subjects with normal hepatic function.
There is limited clinical data on the safety of selpercatinib in patients with severe hepatic impairment. Therefore dose modification is recommended for patients with severe hepatic impairment (see "section *Posology and method of administration"*).

Renal impairment

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

Paediatric population
Based on limited pharmacokinetic data, the Cmax and AUC was similar in adolescent patients, 12-18 years of age, and in adults. Similar exposures were observed in pediatric population of LIBRETTO 121 based on a dose of 92 mg/m2 compared to the adult population in LIBRETTO-001 at a dosage of 160 mg

Preclinical data

Safety pharmacology / toxicity after repeated dose

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

Genotoxicity

Selpercatinib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay, with or without metabolic activation, or clastogenic in the in vitro micronucleus assay in human peripheral lymphocytes, with or without metabolic activation. Selpercatinib was positive at high doses in the in vivo micronucleus assay in rat at approximately 11-fold above the human Cmax at the recommended dose of 160 mg twice daily.
In an in vivo micronucleus assay in rats, selpercatinib was positive at concentrations >7 times the Cmax at the human dose of 160 mg twice daily. In an in vitro micronucleus assay in human peripheral blood lymphocytes, an equivocal response was observed at a concentration approximately 485 times the Cmax at the human dose.

Carcinogenicity

In a 2-year carcinogenicity study of selpercatinib in rats, vaginal tumors were observed in some females at plasma exposure levels similar to levels observed in adult patients treated with the dose of 160 mg twice daily. No pre-neoplastic changes were observed in the reproductive tract of female rats. The clinical relevance of these findings is unknown. Selpercatinib was not carcinogenic in male rats in this study.
Selpercatinib was not carcinogenic in male and female mice in a 6-month study.

Reproductive toxicity

In an embryo-foetal development study, daily oral administration of selpercatinib at doses greater than or equal to 100 mg/kg [approximately 3.6 times the human geometric mean exposure based on the area under the curve (AUC) at the clinical dose of 160 mg twice daily] to pregnant rats during organogenesis resulted in 100% post-implantation loss. At the dose of 50 mg/kg [approximately 1.5 times the human geometric mean exposure based on the AUC at the clinical dose of 160 mg twice daily], 6 of 8 females had 100% early resorptions; the remaining 2 females had primarily early resorptions and only 3 viable foetuses across the 2 litters. The 3 viable foetuses had lower foetal body weight and 2 foetuses in 1 litter had a short tail and the single foetus in the other litter had a small snout and localized foetal edema of the neck and thorax.

Results of studies conducted in rats and minipigs suggest that selpercatinib can impair fertility in males and females.

In a fertility study in male rats, there were no effects of selpercatinib on mating or fertility. However, at all doses, germ cell depletion and spermatid retention in the testes and increased cellular debris in the epididymis were observed dose-dependently. These effects were associated with reduced organ weights, reduced sperm motility, and an increase in the number of abnormal sperm at the highest dose, at which AUC-based exposure was approximately 2.3 times the clinical exposure at the recommended human dose. Microscopic findings in the fertility study in male rats were consistent with effects in repeat dose studies in rats and minipigs, in which dose-dependent, non-reversible testicular degeneration was associated with reduced luminal sperm in the epididymis at AUC-based exposure levels 0.1 to 0.4 times the clinical exposure at the recommended human dose.

In a fertility and early embryonic study in female rats, there were no effects of selpercatinib on mating or fertility. However, at the high dose only, a reduction in the number of estrous cycles with an increase in the pre-coital interval was observed, and there was an increase in the number of dead embryos, increased postimplantation loss, and a reduction in the number of live embryos. These effects were observed at AUC-based exposure levels approximately equal to clinical exposure at the

recommended human dose. In repeat-dose studies in female rats, reversible vaginal mucification with individual cell cornification and altered estrous cycles was noted at clinically relevant AUC-based exposure levels. In female minipigs, decreased corpora lutea and/or corpora luteal cysts were observed at AUC-based exposure levels 0.07 to 0.3 times the clinical exposure at the recommended human dose.

Toxicity tests with juvenile animals
The skeletal changes were observed at exposures approximately equivalent to exposure in adults at the recommended dose of 160 mg twice daily

Juvenile and adolescent rats and adolescent minipigs with open growth plates administered selpercatinib exhibited microscopic changes such as hypertrophy, hyperplasia, and dysplasia of growth plate cartilage (physis). In the study in juvenile rats, these changes at the growth plate were associated with decreased femur length and reductions in bone mineral density.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Do not store above 30°C.

Keep the container in the outer carton in order to protect the contents from moisture. Keep out of the reach of children.

Authorisation number

67’862 (Swissmedic).

Packs

Retsevmo 40 mg: 56 hard capsules (A)
Retsevmo 80 mg: 56 and 112 hard capsules (A)
Not all pack sizes may be marketed.

Marketing authorisation holder

Eli Lilly (Suisse) SA, 1214 Vernier/GE.

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