SUMMARY OF PRODUCT CHARACTERISTICS

▼ 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 adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Retsevmo 80 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Retsevmo 40 mg film-coated tablets

Each film-coated tablet contains 40 mg selpercatinib.

Retsevmo 80 mg film-coated tablets

Each film-coated tablet contains 80 mg selpercatinib.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Retsevmo 80 mg film-coated tablets

Dark red-purple, round tablet debossed on one side with “6082” and debossed with “Ret 80” on the other. The diameter of the tablet is approximately 7.3 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

– advanced *RET* fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a *RET* inhibitor

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

– advanced *RET* fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)

– advanced *RET*-mutant medullary thyroid cancer (MTC)

4.2 Posology and method of administration

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

RET testing

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

Posology

The recommended dose of Retsevmo based on body weight is:

- Less than 50 kg: 120 mg twice daily.

- 50 kg or greater: 160 mg twice daily.

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

Treatment should be continued until disease progression or unacceptable toxicity.

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

Dose adjustments
Management of some adverse reactions may require dose interruption and/or dose reduction. Retsevmo dose modifications are summarised in Table 1 and Table 2.

Table 1 Recommended dose modifications for Retsevmo for adverse reactions based on body weight

Dose modification	**Adults and adolescents ≥50 Kg**	**Adults and adolescents <50 Kg**
Starting dose	160 mg orally twice daily	120 mg orally twice daily
First dose reduction	120 mg orally twice daily	80 mg orally twice daily
Second dose reduction	80 mg orally twice daily	40 mg orally twice daily
Third dose reduction	40 mg orally twice daily	Not applicable

Table 2 Recommended dose modifications for adverse reactions

Adverse drug reaction (ADR)		**Dose modification**
Increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST)	Grade 3 or Grade 4	• Suspend dose until toxicity resolves to baseline (see sections 4.4 and 4.8). Resume at a dose reduced by 2 levels. • If after at least 2 weeks selpercatinib is tolerated without recurrent increased ALT or AST, increase dosing by 1 dose level. • If selpercatinib is tolerated without recurrence for at least 4 weeks, increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT. • Permanently discontinue selpercatinib if Grade 3 or 4 ALT or AST increases recur despite dose modifications.
Hypersensitivity	All Grades	• Suspend dose until toxicity resolves and begin corticosteroids at a dose of 1 mg/kg (see sections 4.4 and 4.8). Resume selpercatinib at 40 mg twice daily while continuing steroid treatment. Discontinue selpercatinib for recurrent hypersensitivity. • If after at least 7 days, selpercatinib is tolerated without recurrent hypersensitivity, incrementally increase the selpercatinib dose by 1 dose level each week, until the dose taken prior to the onset of hypersensitivity is reached. Taper steroid dose after selpercatinib has been tolerated for at least 7 days at the final dose.
QT interval prolongation	Grade 3	• Suspend dose for QTcF intervals >500 ms until the QTcF returns to <470 ms or baseline (see section 4.4). • Resume selpercatinib treatment at the next lower dose level.
	Grade 4	• Permanently discontinue selpercatinib if QT prolongation remains uncontrolled after two dose reductions or if the patient has signs or symptoms of serious arrhythmia.

Hypertension	Grade 3	• Patient blood pressure should be controlled before starting treatment. • Selpercatinib should be suspended temporarily for medically significant hypertension until controlled with antihypertensive therapy. Dosing should be resumed at the next lower dose if clinically indicated (see sections 4.4 and 4.8).
	Grade 4	• Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled.
Haemorrhagic events	Grade 3	• Selpercatinib should be suspended until recovery to baseline. Resume at a reduced dose. If Grade 3 events reoccur following dose modification, permanently discontinue selpercatinib.
	Grade 4	• Permanently discontinue selpercatinib.
Interstitial lung disease (ILD)/Pneumonitis	Grade 2	• Withhold selpercatinib until resolution. • Resume at a reduced dose. • Discontinue selpercatinib for recurrent ILD/pneumonitis
	Grade 3 or Grade 4	• Discontinue selpercatinib.
Other adverse reactions	Grade 3 or Grade 4	• Selpercatinib should be suspended until recovery to baseline. Resume at a reduced dose. • If Grade 4 events reoccur following dose modification, permanently discontinue selpercatinib.

Special populations

Elderly
No dose adjustment is required based on age (see section 5.2).
No overall differences were observed in the treatment emergent adverse events or effectiveness of selpercatinib between patients who were ≥65 years of age and younger patients. Limited data are available in patients ≥75 years.

Renal impairment
Dose adjustment is not necessary in patients with mild, moderate or severe renal impairment. There are no data in patients with end stage renal disease, or in patients on dialysis (section 5.2).

Hepatic impairment
Close monitoring of patients with impaired hepatic function is important. No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Patients with severe (Child-Pugh class C) hepatic impairment should be dosed with 80 mg selpercatinib twice daily (section 5.2).

Paediatric population
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.
Retsevmo is intended to be used from the age of 12 years for the treatment of patients with RET-mutant MTC and RET fusion-positive thyroid cancer (see section 5.1). In RET-mutant MTC and RET fusion-positive thyroid cancer, there are very limited data available in children or adolescents aged less than 18 years. Patients should be dosed according to body weight (see section 4.2). Based on results from a preclinical study (see section 5.3), open growth plates in adolescent patients should be monitored. Dose interruption or discontinuation should be considered based on the severity of any growth plate abnormalities and an individual risk-benefit assessment.

Method of administration

Retsevmo is for oral use.

The tablets should be swallowed whole to ensure consistent performance (patients should not crush, chew, or split the tablet before swallowing), and can be taken with or without food. In case of difficulty swallowing the larger tablets whole, patients may consider taking multiple units of the smaller tablets to achieve the required dose.
Patients should take the doses at approximately the same time every day.
Retsevmo must be accompanied by a meal if used concomitantly with a proton pump inhibitor (see section 4.5).
Retsevmo should be administered 2 hours before or 10 hours after H_2 receptor antagonists (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal cases of ILD/pneumonitis have been reported in patients treated with selpercatinib (see section 4.8). Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Selpercatinib should be withheld, and patients should be promptly investigated for ILD if they present with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnoea, cough, and fever), and treated as

medically appropriate. Based on the severity of ILD/pneumonitis, the dose of selpercatinib should be interrupted, reduced, or permanently discontinued (see section 4.2).

Increased alanine aminotransferase (ALT)/ aspartate aminotransferase (AST)

Grade ≥3 increased ALT and Grade ≥3 increased AST were reported in patients receiving selpercatinib (see section 4.8). ALT and AST should be monitored prior to the start of selpercatinib therapy, every 2 weeks during the first 3 months of treatment, monthly for the next 3 months of treatment, and otherwise as clinically indicated. Based on the level of ALT or AST elevations, selpercatinib may require dose modification (see section 4.2).

Hypertension

Hypertension was reported in patients receiving selpercatinib (see section 4.8). Patient blood pressure should be controlled before starting selpercatinib treatment, monitored during selpercatinib treatment and treated as needed with standard anti-hypertensive therapy. Based on the level of increased blood pressure, selpercatinib may require dose modification (see section 4.2). Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled with antihypertensive therapy.

QT interval prolongation

QT interval prolongation was reported in patients receiving selpercatinib (see section 5.1). Selpercatinib should be used with caution in patients with such conditions as congenital long QT syndrome or acquired long QT syndrome or other clinical conditions that predispose to arrhythmias.
Patients should have a QTcF interval of ≤470 ms and serum electrolytes within normal range before starting selpercatinib treatment. Electrocardiograms and serum electrolytes should be monitored in all patients after 1 week of selpercatinib treatment, at least monthly for the first 6 months and otherwise, as clinically indicated, adjusting frequency based upon risk factors including diarrhoea, vomiting, and/or nausea. Hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiating selpercatinib and during treatment. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medicinal products known to prolong the QT interval.
Selpercatinib may require dose interruption or modification (see section 4.2).

Hypothyroidism

Hypothyroidism has been reported in patients receiving selpercatinib (see section 4.8). Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism should be treated as per standard medical practice prior to the start of selpercatinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction during selpercatinib treatment. Thyroid function should be monitored periodically throughout treatment with selpercatinib. Patients who develop thyroid dysfunction should be treated as per standard medical practice, 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 (see section 4.5).

Strong CYP3A4 inducers

Concomitant use of strong CYP3A4 inducers should be avoided due to the risk of decreased efficacy of selpercatinib (see section 4.5).

Women of childbearing potential/Contraception in females and males

Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose of selpercatinib. Men with female partners of childbearing potential should use effective contraception during treatment and for at least one week after the last dose of selpercatinib (see section 4.6).

Fertility

Based on nonclinical safety findings, male and female fertility may be compromised by treatment with Retsevmo (see sections 4.6 and 5.3). Both men and women should seek advice on fertility preservation before treatment.

Hypersensitivity

Hypersensitivity was reported in patients receiving selpercatinib with a majority of events observed in patients with NSCLC previously treated with anti-PD-1/PD-L1 immunotherapy (see section 4.8). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or elevated aminotransferases.
Suspend selpercatinib if hypersensitivity occurs, and begin steroid treatment. Based on the grade of hypersensitivity reactions, selpercatinib may require dose modification (see section 4.2). Steroids should be continued until patient reaches target dose and then tapered. Permanently discontinue selpercatinib for recurrent hypersensitivity.

Haemorrhages

Serious including fatal haemorrhagic events were reported in patients receiving selpercatinib (see section 4.8).
Permanently discontinue selpercatinib in patients with life-threatening or recurrent severe haemorrhage (see section 4.2).

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.

Epiphysiolysis of the femoral head in Paediatric Patients

Epiphysiolysis of the femoral head has been reported in paediatric patients (<18 years of age) receiving selpercatinib (see section 4.8). Patients should be monitored for symptoms indicative of epiphysiolysis of the femoral head and treated as medically and surgically appropriate.

Severe cutaneous adverse reactions (SCARs)

Stevens-Johnson syndrome (SJS), which can be life-threatening or fatal, has been reported in association with selpercatinib treatment (see section 4.8). Patients should be advised of the signs of the severe cutaneous adverse reactions and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. If signs and symptoms suggestive of these reactions appear, selpercatinib should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has

developed a severe cutaneous adverse reaction such as SJS with the use of selpercatinib, treatment with selpercatinib must not be restarted in this patient at any time.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on the pharmacokinetics of selpercatinib

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

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_{0-24} and C_{max}, respectively).

Agents that may increase selpercatinib plasma concentrations
Co-administration of a single 160 mg selpercatinib dose with itraconazole, a strong CYP3A inhibitor, 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, telithromycin, posaconazole and nefazodone, have to be co-administered, the dose of selpercatinib should be reduced (see section 4.2).

Agents that may decrease selpercatinib plasma concentrations
Co-administration of rifampicin, a strong CYP3A4 inducer resulted in a decrease of approximately 87% and 70% in selpercatinib AUC and C_{max}, 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.

Effects of selpercatinib on the pharmacokinetics of other medicinal products (increase in plasma concentration)

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

Sensitive CYP3A4 substrates
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, buspirone, conivaptan, darifenacin,

darunavir, ebastine, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, tipranavir, triazolam, vardenafil), should be avoided.

Co-administration with medicinal products that affect gastric pH

Selpercatinib has pH-dependent solubility, with decreased solubility at higher pH. No clinically significant differences in selpercatinib pharmacokinetics were observed when co-administered with multiple daily doses of ranitidine (H_2 receptor antagonist) given 2 hours after the selpercatinib dose.

Co-administration with medicinal products that are proton pump inhibitors

Co-administration with multiple daily doses of omeprazole (a proton pump inhibitor) decreased selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when selpercatinib was administered fasting. Co-administration 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.

Co-administration 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 (see section 5.2).

Selpercatinib is an *in vitro* inhibitor of P-gp and 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 5.2).

Medicinal products that may be less effective when given with selpercatinib

Selpercatinib could inhibit D2 deiodinase and thereby decrease the conversion of levothyroxine (T4) to triiodothyronine (T3). Patients could therefore have an insufficient response to substitution with levothyroxine and supplementation with liothyronine may be needed (see section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females and males

Women of childbearing potential have to use highly effective contraception during treatment and for at least one week after the last dose of selpercatinib. Men with female partners of childbearing potential should use effective contraception during treatment and for at least one week after the last dose of selpercatinib.

Pregnancy

There are no available data from the use of selpercatinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Retsevmo is not recommended during pregnancy and in women of childbearing potential not using contraception. It should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

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

Fertility

No human data on the effect of selpercatinib on fertility are available. Based on findings from animal studies, male and female fertility may be compromised by treatment with Retsevmo (see section 5.3). Both men and women should seek advice on fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The integrated frequency of adverse drug reactions (ADRs) reported in patients treated with selpercatinib from an open-label, multicentre, dose-escalation phase 1/2 study (LIBRETTO-001) and from two open-label, multicentre, randomised phase 3 comparative studies (LIBRETTO-431 and LIBRETTO-531) are summarised. The most common (≥ 1.0%) serious ADRs are pneumonia (5.3%), haemorrhage (2.4%), abdominal pain (2.1%), blood sodium decreased (2.0%), diarrhoea (1.5%), hypersensitivity (1.4%), vomiting (1.3%), blood creatinine increased (1.3%), pyrexia (1.3%), urinary tract infections (1.3%), ALT increased (1.0%) and AST increased (1.0%).
Permanent discontinuation of Retsevmo for treatment emergent adverse events, regardless of attribution occurred in 8.8% of patients. The most common ADRs resulting in permanent discontinuation (3 or more patients) were increased ALT (0.7%), fatigue (0.5%), increased AST (0.4%), blood bilirubin increased (0.3%), pneumonia (0.3%), thrombocytopenia (0.3%), haemorrhage (0.3%), and hypersensitivity (0.3%).

Tabulated list of adverse drug reactions

The integrated frequency and severity of ADRs reported in patients treated with selpercatinib in Study LIBRETTO-001, Study LIBRETTO-431, and Study LIBRETTO-531 are shown in Table 3.

The ADRs are classified according to the MedDRA system organ class and frequency.

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).

Median time on treatment with selpercatinib was 30.09 months (Study LIBRETTO-001), 16.7 months (Study LIBRETTO-431), and 14.9 months (Study LIBRETTO-531).

Table 3 Adverse drug reactions in patients receiving selpercatinib (N=1188)

MedDRA system organ class	MedDRA preferred term	Frequency of all Grades	Frequency of Grade ≥ 3
Infections and infestations	Urinary tract infections[a]	Very common	Common
	Pneumonia[b]	Very common	Common
Immune system disorders[c]	Hypersensitivity[d]	Common	Common
Endocrine disorders	Hypothyroidism	Very common	-
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Nervous system disorders	Headache[e]	Very common	Common
	Dizziness[f]	Very common	Uncommon
Cardiac disorders	Electrocardiogram QT prolonged[g]	Very common	Common
Vascular disorders	Hypertension[h]	Very common	Very common
	Haemorrhage[i]	Very common	Common
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease/pneumonitis[j]	Common	Uncommon
	Chylothorax	Common	Uncommon
Gastrointestinal disorders	Diarrhoea[k]	Very common	Common
	Dry Mouth[l]	Very common	Uncommon
	Abdominal pain[m]	Very common	Common
	Constipation	Very common	Uncommon
	Nausea	Very common	Common
	Vomiting[n]	Very common	Common
	Stomatitis[o]	Very common	Uncommon
	Chylous ascites[p]	Common	Uncommon
Skin and subcutaneous tissue disorders	Rash[q]	Very common	Common
	Stevens-Johnson Syndrome[r]	Not known	Not known
Musculoskeletal and connective tissue disorders	Epiphysiolysis of the femoral head[s]	Common	Common
Reproductive system and breast disorders	Erectile dysfunction[t]	Very common	Uncommon
General disorders and administration site conditions	Oedema[u]	Very common	Common
	Fatigue[v]	Very common	Common
	Pyrexia	Very common	Uncommon
Investigations[w]	AST increased	Very common	Very common
	ALT increased	Very common	Very common
	Calcium decreased	Very common	Common

MedDRA system organ class	MedDRA preferred term	Frequency of all Grades	Frequency of Grade ≥ 3
	Lymphocyte count decreased	Very common	Very common
	White blood cell count decreased	Very common	Common
	Albumin decreased	Very common	Common
	Creatinine increased	Very common	Common
	Sodium decreased	Very common	Very common
	Alkaline phosphatase increased	Very common	Common
	Platelets decreased	Very common	Common
	Total bilirubin increased	Very common	Common
	Neutrophil count decreased	Very common	Common
	Haemoglobin decreased	Very common	Common
	Magnesium decreased	Very common	Common
	Potassium decreased	Very common	Common

[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, vessel puncture site haematoma, haemarthrosis and haematoma.

[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] From post-marketing data.

[s] Epiphysiolysis of the femoral head has been commonly observed (6.4%) in paediatric patients (<18 years of age) treated with selpercatinib (n=47).

[t] Erectile dysfunction has been very commonly observed (12.4%) in male patients treated with selpercatinib in clinical trials (n=986).

[u] 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 oedema, periorbital swelling and swelling of eyelid.

[v] Fatigue includes fatigue, asthenia and malaise.

[w] 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 adverse reactions in patients receiving selpercatinib

Aminotransferase elevations (AST / ALT increased)
Based on laboratory assessment, ALT and AST elevations were reported in 59.4% and 61% patients, respectively. Grade 3 or 4 ALT or AST elevations were reported in 14.1% and 9.5% patients respectively.
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, AST increase 5.1 weeks (range: 0.7, 88.1), ALT increase 5.1 weeks (range: 0.7, 110.9) in LIBRETTO-431, and AST increase 6.1 weeks (range: 0.1, 85.1), ALT increase 6.1 weeks (range: 0.1, 85.1) in LIBRETTO-531.
Dose modification is recommended for patients who develop Grade 3 or 4 ALT or AST increase (see section 4.2).

QT interval prolongation
In the 837 patients in study LIBRETTO-001 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 maximum increase from baseline in QTcF intervals. In the 156 patients in LIBRETTO-431 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 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.

In LIBRETTO-001, LIBRETTO-431 and LIBRETTO-531 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 sections 4.2 and 4.4).

Hypertension
In the 837 patients who had blood pressure measurements in study LIBRETTO-001, 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. A treatment emergent adverse event of hypertension was reported in 44.8% patients with history of hypertension (28.2% with grade 3, 4) and 41.7% of patients without history of hypertension (14.1% with grade 3, 4).
In the 154 patients treated with selpercatinib who had blood pressure measurements in LIBRETTO-431, 23.4% of patients treated with selpercatinib retained their baseline grade during treatment, 49.4% had an increasing shift of 1 grade, 22.7% had an increasing shift of 2 grades, and 3.3% had an increasing shift of 3 grades.
In the 192 patients treated with selpercatinib who had blood pressure measurements in LIBRETTO-531, 20.8% of patients treated with selpercatinib retained their baseline grade during treatment, 43.8% had an increasing shift of 1 grade, 27.6% had an increasing shift of 2 grades, and 6.8% had an increasing shift of 3 grades.
Overall, a total of 19.8% of patients in LIBRETTO-001, 20.3% of patients in LIBRETTO-431, and 19.2% of patients in LIBRETTO-531 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, and no reports in LIBRETTO-431 and LIBRETTO-531.
Two patients (0.2%) permanently discontinued treatment due to hypertension in LIBRETTO-001, and no patients in LIBRETTO-431 and LIBRETTO-531. Dose modification is recommended in patients who develop hypertension (see section 4.2). Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled with antihypertensive therapy (see section 4.4).

Hypersensitivity
Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or increased aminotransferase.
In study LIBRETTO-001, 24.0% (201/837) of patients treated with selpercatinib had previously received anti-PD-1/PD-L1 immunotherapy. Hypersensitivity occurred in a total of 5.7% (48/837) of patients receiving selpercatinib, including Grade 3 hypersensitivity in 1.9% (16/837) of patients.
Of the 48 patients with hypersensitivity in LIBRETTO-001, 54.2% (26/48) had NSCLC and had received prior anti-PD-1/PD-L1 immunotherapy.
Grade 3 hypersensitivity occurred in 3.5% (7/201) of the patients previously treated with anti-PD-1/PD-L1 immunotherapy in LIBRETTO-001.
In LIBRETTO-001, the median time to onset was 1.9 weeks (range: 0.7 to 203.9 weeks): 1.7 weeks in patients with previous anti-PD-1/PD-L1 immunotherapy and 4.4 weeks in patients who were anti-PD-1/PD-L1 immunotherapy naïve.
Study LIBRETTO-431 enrolled patients with advanced or metastatic NSCLC. Hypersensitivity occurred in a total of 1.9% (3/158) of patients receiving selpercatinib, including Grade 3 hypersensitivity in 0.6% (1/158) of patients. In an integrated analysis of patients with NSCLC receiving selpercatinib who were previously treated with anti-PD-1/PD-

L1 therapy based on studies LIBRETTO-001 and LIBRETTO-431 (N=205), hypersensitivity occurred in 16.6% of patients, including ≥Grade 3 hypersensitivity in 5.9% of patients. Study LIBRETTO-531 enrolled patients with advanced or metastatic MTC. Hypersensitivity occurred in 1 patient (0.5% [1/193]) receiving selpercatinib. This 1 patient experienced Grade 3 hypersensitivity.
Retsevmo may require dose interruption or modification (see section 4.2).

Haemorrhages
Grade ≥3 haemorrhagic events occurred in 2.5% of patients treated with selpercatinib across studies LIBRETTO-001, LIBRETTO-431 and LIBRETTO-531. In LIBRETTO-001 this included 4 (0.5%) patients with fatal haemorrhagic events, two cases of cerebral haemorrhage, and one case each of tracheostomy site haemorrhage, and haemoptysis. No fatal haemorrhagic events were reported in patients treated with selpercatinib in LIBRETTO-431 or LIBRETTO-531. The median time to onset was 34.1 weeks (range: 0.1 week to 234.6 weeks) in LIBRETTO-001, 16.8 weeks (range: 1.1 to 94.1 weeks) in LIBRETTO-431, and 10.7 weeks (range: 1.0 to 124.1 weeks) in LIBRETTO-531.
Selpercatinib should be discontinued permanently in patients with life-threatening or recurrent severe haemorrhage (see section 4.2).

Additional information on special populations

Paediatric patients
There were 3 patients < 18 years (range: 15-17) of age with RET-mutant MTC in LIBRETTO-001. There were 8 patients < 18 years (range 12-17) of age with RET fusion-positive thyroid cancer in LIBRETTO-121. There was 1 patient 12 years of age with RET-mutant MTC in LIBRETTO-531. Cases of epiphysiolysis of the femoral head have been reported in patients < 18 years of age treated with selpercatinib (see section 4.4). No other unique safety findings in children aged less than 18 years have been identified.

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. In study LIBRETTO-431, 26.6% of patients receiving selpercatinib were ≥65-74 years of age, 9.5% were 75-84 years of age and 1.3% were ≥85 years of age. In study LIBRETTO-531, 20.2% of patients receiving selpercatinib were ≥65-74 years of age, 5.2% were 75-84 years of age and none were ≥85 years of age. The frequency of serious adverse events reported was higher in patients ≥65-74 years (58.0%), 75-84 years (62.5%), and ≥85 years (100.0%), than in patients <65 years (46.7%) of age in LIBRETTO-001 and in LIBRETTO-431, ≥65-74 years (38.1%), 75-84 years (46.7%), ≥85 years (50.0%), than in patients <65 years (31.3%) of age. In LIBRETTO-531 the frequency of serious adverse events reported was higher in patients 75-84 years (50%) than in patients <65 years (20.8%) and 65-74 years (17.9%).
In study LIBRETTO-001 the frequency of adverse events (AE) leading to discontinuation of selpercatinib was higher in patients ≥65-74 years (10.1%), 75-84 years (19.4%), and ≥85 years (37.5%), than in patients <65 years of age (7.6%). In study LIBRETTO-431, the frequency of AE leading to discontinuation of selpercatinib was higher in patients ≥65-74 years (14.3%), 75-84 years (20.0%) than in patients <65 years (7.1%) of age. No patients ≥85 years of age discontinued selpercatinib due to AE. In LIBRETTO-531, the frequency of AE leading to discontinuation of selpercatinib was higher in patients 75-84 years (10%), and ≥65-74 years (7.7%) than in patients <65 years (3.5%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow

Card Scheme, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, protein kinase inhibitors, ATC code: L01EX22

Mechanism of action

Selpercatinib is an 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. In a binding assay at the concentration of 1 µM selpercatinib, significant antagonist binding activity (>50%) was observed for the 5-HT (serotonin) transporter (70.2% antagonist) and α2C adrenoreceptor (51.7% antagonist). The concentration of 1 µM is approximately 7-fold higher than the maximum unbound plasma concentration of at the efficacious dose of selpercatinib.
Certain point mutations in RET or chromosomal rearrangements involving in-frame fusions of RET with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers by promoting cell proliferation of tumour cell lines. In *in vitro* and *in vivo* tumour models, selpercatinib demonstrated anti-tumour activity in cells harboring constitutive activation of RET protein resulting from gene fusions and mutations, including CCDC6-RET, KIF5B-RET, RET V804M, and RET M918T. In addition, selpercatinib showed anti-tumour activity in mice intracranially implanted with a patient-derived RET fusion-positive tumour.

Pharmacodynamic properties

Cardiac electrophysiology
In a thorough QT study with positive control in 32 healthy subjects, no large change (that is, >20 ms) in the QTcF interval was detected at selpercatinib concentrations similar to those observed with a therapeutic dosing schedule. 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 sections 4.2 and 4.4).

Clinical efficacy and safety

The efficacy of Retsevmo was evaluated in adult patients with advanced RET fusion-positive NSCLC and RET fusion-positive thyroid cancer, and in adult and adolescent patients with RET-mutant MTC enrolled in a phase 1/2, multicenter, open-label, single-arm clinical study: Study LIBRETTO-001. Efficacy of Retsevmo in RET fusion-positive NSCLC was confirmed in the Phase 3 Study LIBRETTO-431 (see section Treatment-naïve RET fusion-positive NSCLC). Efficacy of Retsevmo in RET-mutant MTC was confirmed in the Phase 3 Study LIBRETTO-531 (see section Vandetanib and cabozantinib naïve RET-mutant medullary thyroid cancer (MTC)).

Study LIBRETTO-001 included two parts: phase 1 (dose escalation) and phase 2 (dose expansion). The primary objective of the phase 1 portion was to determine the recommended phase 2 dose of selpercatinib. The primary objective of the phase 2 part was to evaluate the anti-tumour activity of selpercatinib by determining objective response rate (ORR), as assessed by independent review committee. Patients with measurable or non-measurable disease as determined by RECIST 1.1, with evidence of a RET gene alteration in tumour were enrolled. Patients with central nervous system (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 primary efficacy outcome measure was ORR according to RECIST v1.1 as evaluated by a Blinded Independent Review Committee (IRC). Secondary efficacy outcomes included duration of response (DOR), progression free survival (PFS) and overall survival (OS).

Treatment-naïve RET fusion-positive NSCLC

LIBRETTO-431
The efficacy of Retsevmo in RET fusion-positive NSCLC was confirmed in LIBRETTO-431, a phase 3 multicentre, randomised, open-label comparator 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 received 160 mg of selpercatinib twice daily (starting dose) or platinum-based and pemetrexed therapy with or without pembrolizumab. 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 blinded independent central review (BICR). Secondary efficacy outcomes included OS, ORR/DOR/Disease Control Rate (DCR) by BICR, intracranial ORR/DOR by BICR, and time to deterioration in pulmonary symptoms by NSCLC-Symptom Assessment Questionnaire (SAQ).

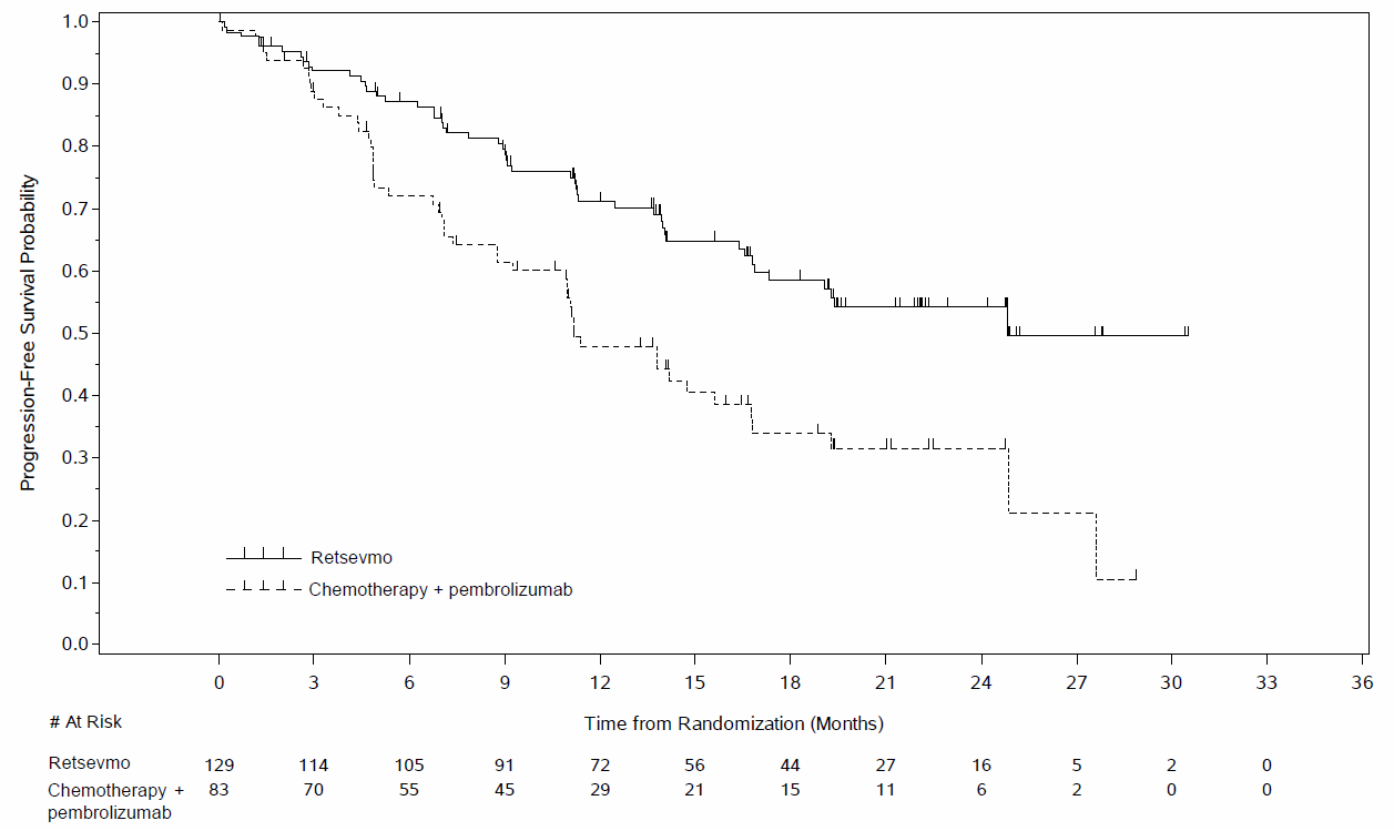
Of the 261 patients enrolled and randomized in Study LIBRETTO-431 intention to treat (ITT) population, 212 were stratified according to whether the investigator would intend for the patient to receive pembrolizumab (before randomisation), to form the ITT-Pembrolizumab population. In the ITT-Pembrolizumab 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 endpoint of improving PFS in both the ITT-Pembrolizumab and ITT populations. Primary efficacy results for the ITT-Pembrolizumab population for treatment naïve patients with RET fusion-positive NSCLC are summarised in Table 4 and Figure 1.

Table 4 LIBRETTO-431: Summary of efficacy data (BICR assessment, ITT-Pembrolizumab population)

	Selpercatinib	**Control (platinum-based pemetrexed chemotherapy with pembrolizumab)**
Progression-free survival	**N = 129**	**N = 83**
Median [months] (95% CI)	24.84 (16.89, NE)	11.17 (8.77, 16.76)
Hazard ratio (95% CI)	0.465 (0.309, 0.699)	
Stratified log rank p-value	0.0002	
24 months PFS rate (%) (95% CI)	54.2 (43.6, 63.6)	31.6 (20.1, 43.7)
Objective response (CR + PR)		
% (95% CI)	83.7 (76.2, 89.6)	65.1 (53.8, 75.2)
Complete response n (%)	9 (7.0)	5 (6.0)
Partial response n (%)	99 (76.7)	49 (59.0)
Duration of response*		
Median [months] (95% CI)	24.18 (17.94, NE)	11.47 (9.66, 23.26)
Rate (%) of patients with duration of response		
24 months (95% CI)	59.6 (47.5, 69.8)	22.8 (6.3, 45.5)

CI = Confidence Interval, NE = not estimable, CR = complete response, PR = partial response
*Median duration of follow-up was 17.97 months (25^{th}, 75^{th} percentile: 12.32, 21.03) in the selpercatinib arm and 14.55 months (25^{th}, 75^{th} percentile: 9.69, 20.73) in the control arm.
Data Cut-off date: 01 May 2023

Figure 1. LIBRETTO-431: Kaplan-Meier plot of progression-free survival (BICR assessment, ITT-Pembrolizumab population)



Data Cut-off date: 01 May 2023

OS was not mature at the time of the primary PFS analysis. At the time of an updated descriptive interim analysis of OS (43% of prespecified OS events needed for the final analysis, with a data lock of 1 May 2024), in the ITT population, 75 events were observed across the two arms and the Hazard Ratio (HR) was 1.259 ([95% CI: 0.777, 2.040]; p=0.3496). At 30 months the estimated overall survival was 71% (95% CI: 63, 78) and 76% (95% CI: 66, 84) in the selpercatinib arm and the control arm, respectively. OS may be affected by the imbalance in post-progression therapies. 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.

In the ITT-Pembrolizumab population, selpercatinib significantly delayed time to worsening of patient-reported NSCLC symptoms, as measured by the NSCLC-SAQ total score (≥ 2-point increase) compared with the control (HR: 0.34 [95% CI: 0.20, 0.55]; median time was not reached for selpercatinib arm versus 1.9 months [95% CI: 0.7, 6.6]) for the control arm. In addition, selpercatinib significantly delayed time to confirmed deterioration of physical function and maintained overall quality of life over time.

LIBRETTO-001

Of the 362 *RET* fusion-positive NSCLC patients enrolled in LIBRETTO-001, 69 were treatment naïve. The median age was 63 years (range 23 years to 92 years). 62.3% of patients were female. 69.6% of patients were White, 18.8% were Asian, 5.8% were Black and 69.6% were never smokers. Most patients (98.6%) had metastatic disease at enrolment and 23.2% had CNS metastasis at baseline as assessed by investigator. ECOG performance status was reported as 0-1 (94.2%) or 2 (5.8%).

The most common fusion partner was KIF5B (69.6%), followed by CCDC6 (14.5%) and then NCOA4 (1.4%). Efficacy results for treatment-naive RET fusion-positive NSCLC patients are summarised in Table 5.

Table 5 LIBRETTO-001: Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	69
Objective response (CR + PR)	
% (95% CI)	82.6 (71.6, 90.7)
Complete response n (%)	5 (7.2)
Partial response n (%)	52 (75.4)
Duration of response (months)*	
Median, 95% CI	20.23 (15.4, 29.5)
Rate (%) of patients with duration of response	
≥ 6 months (95% CI)	87.5 (75.5, 93.8)
≥ 12 months (95% CI)	66.7 (52.4, 77.6)

CI = Confidence Interval, CR = complete response, PR = partial response
*Median duration of follow-up was 37.09 months (25^{th}, 75^{th} percentile: 24.0, 45.1)
Data Cut-off date: 13 January 2023

Previously treated RET fusion-positive NSCLC

A total of 247 patients had received prior platinum-based chemotherapy in Study LIBRETTO-001. 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 0-1 (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%). 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/PD-L1 therapy (58.3%), multi-kinase inhibitor (MKI) (31.6%) and taxanes (34.8%); 41.3% had other systemic therapy. Efficacy results for previously treated RET fusion-positive NSCLC patients are summarised in Table 6.

Table 6 LIBRETTO-001: Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	247
Objective response (CR + PR)	
% (95% CI)	61.5 (55.2, 67.6)
Complete response n (%)	20 (8.1)
Partial response n (%)	132 (53.4)
Duration of response (months)*	
Median (95% CI)	31.6 (20.4, 42.3)
Rate (%) of patients with duration of response	
≥ 6 months (95% CI)	87.0 (80.4, 91.5)
≥ 12 months (95% CI)	73.0 (65.0, 79.5)

CI = Confidence Interval, CR = complete response, PR = partial response
*Median duration of follow-up was 39.52 months (25^{th}, 75^{th} percentile: 24.6, 45.0)
Data Cut-off date: 13 January 2023

CNS response in RET fusion-positive NSCLC

In Study LIBRETTO-431 the CNS ORR assessed by BICR was 82.4% (14/17 95% CI: 56.6, 96.2) in the 17 patients with measurable brain metastases at baseline treated with selpercatinib, versus 58.3% (7/12 95% CI: 27.7 to 84.4) in the 12 patients in the control arm of the ITT-Pembrolizumab population. CR was observed in 6/17 (35.3%) of patients in the selpercatinib arm versus 2/12 (16.7%) patients in the control arm. With a median follow up time for DOR of 9.92 months (95% CI: 7.66, 18.10) in the selpercatinib arm and 12.68 months (95% CI: 2.79, NE) in the control arm, the median DOR was not reached for selpercatinib (95% CI: 7.62, NE) compared to 13.4 months (95% CI: 3.45, NE) with control. In 192 patients with intracranial baseline scans available, the cause-specific hazard ratio for the time to CNS progression, as assessed by BICR, was 0.28; 95% CI: 0.12, 0.68 (HR of 0.17; 95% CI: 0.04, 0.69 for 150 patients without baseline intracranial metastases, and HR of 0.61; 95% CI: 0.19, 1.92 for 42 patients with baseline intracranial metastases). 8 patients (6.7%) in the selpercatinib arm had a first event of CNS progression compared to 13 patients (18.1%) in the control arm.

The CNS ORR assessed by IRC was 84.6% (22/26; 95% CI: 65.1, 95.6) in 26 patients with measurable disease in Study LIBRETTO-001. CR was observed in 7 (26.9%) patients and PR in 15 (57.5%) patients. The median CNS DOR was 9.36 months (95% CI: 7.4, 15.3).

Systemic treatment-naive RET fusion-positive thyroid cancer

Of the *RET* fusion-positive thyroid cancer patients naive to systemic therapy other than radioactive iodine, and enrolled in LIBRETTO-001, 24 patients had the opportunity to be followed for at least 6 months and were considered efficacy eligible. The median age was 60.5 years (range 20 to 84 years). 58.3% of patients were male. 75% of patients were White. ECOG performance status was reported as 0-1 (95.8%) or 2 (4.2%). 100% of patients had a history of metastatic disease. 22 out of the 24 patients (91.7%) received radioactive iodine prior to enrolment and therefore were considered radioactive iodine refractory. The different histologies represented in the 24 patients included: papillary (n=23) and poorly differentiated (n=1). The most common fusion partner was CCDC6 (62.5%) followed by NCOA4 (29.2%). Efficacy results for systemic treatment-naive *RET* fusion-positive thyroid cancer patients are summarised in Table 7.

Table 7 LIBRETTO-001: Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	24
Objective response (CR + PR)	
% (95% CI)	95.8 (78.9, 99.9)
Complete response n (%)	5 (20.8)
Partial response n (%)	18 (75.0)
Duration of response (months)*	
Median (95% CI)	NE (42.8, NE)
Rate (%) of patients with duration of response	

	Efficacy eligible patients IRC assessment
N	24
≥ 12 months (95% CI)	100.0 (100.0, 100.0)
≥ 24 months (95% CI)	94.4 (66.6, 99.2)
≥ 36 months (95% CI)	88.9 (62.4, 97.1)

CI = Confidence Interval, CR = complete response, NE = not estimable, PR = partial response
*Median duration of follow-up was 54.80 months (25^{th}, 75^{th} percentile: 32.3, 62.5)
Data Cut-off date: 14 February 2025

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, 41 patients had the opportunity to be followed for at least 6 months and were considered efficacy eligible. 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%). 9.8% had other systemic therapy. The different histologies represented in the 41 patients included: papillary (n = 31), poorly differentiated (n = 5), anaplastic (n = 4), and Hurthle cell (n = 1). The most common fusion partner was CCDC6 (61.0%) followed by NCOA4 (19.5%).

Efficacy results for previously treated RET fusion-positive thyroid cancer are summarised in Table 8.

Table 8 LIBRETTO-001: Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	41
Objective response (CR + PR)	
% (95% CI)	85.4 (70.8, 94.4)
Complete response n (%)	5 (12.2)
Partial response n (%)	30 (73.2)
Duration of response (months)*	
Median (95% CI)	26.7 (12.1, NE)
Rate (%) of patients with duration of response	
≥ 12 months (95% CI)	71.7 (52.4, 84.2)
≥ 24 months (95% CI)	50.7 (30.4, 67.8)

CI = Confidence Interval, CR = complete response, NE = not estimable, PR = partial response
*Median duration of follow-up was 33.87 months (25^{th}, 75^{th} percentile: 12.9, 44.8)
Data Cut-off date: 13 January 2023

Vandetanib and cabozantinib naïve RET-mutant medullary thyroid cancer (MTC)

LIBRETTO-531

The efficacy of Retsevmo in *RET*-mutant MTC was confirmed 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 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). 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, and other secondary efficacy outcomes included OS and ORR/DOR by BICR.

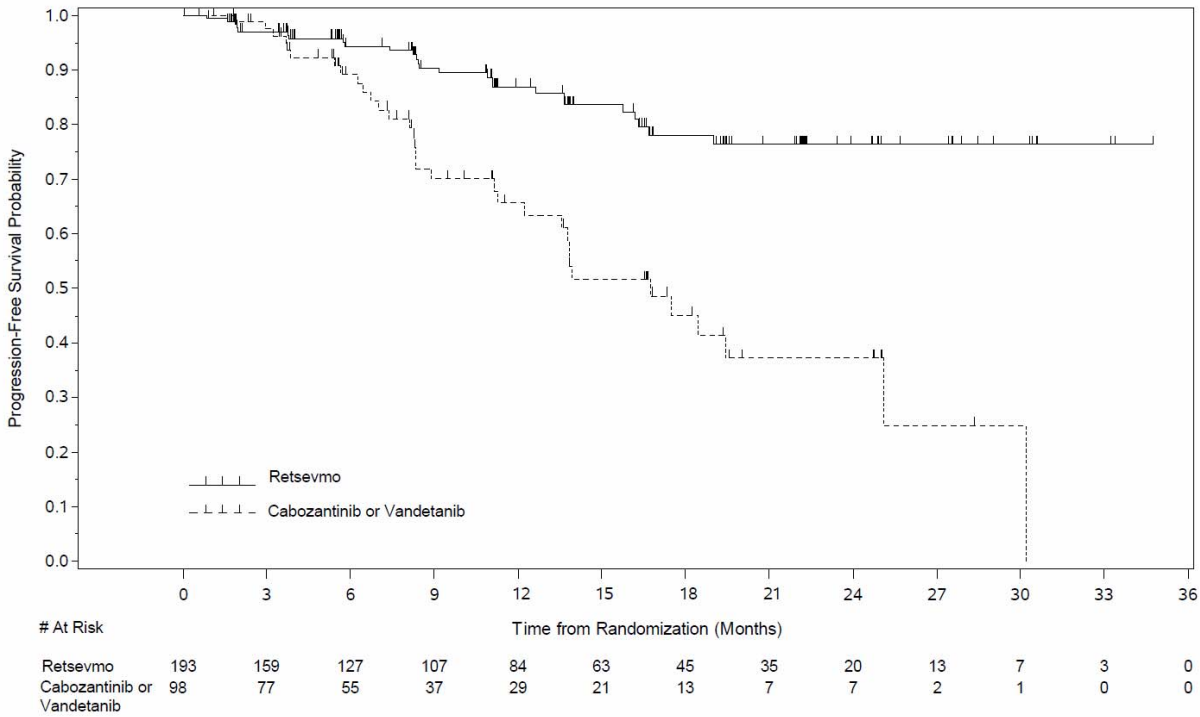
Of the 291 patients enrolled and randomised in LIBRETTO-531 to form the ITT population, 193 were randomised to the selpercatinib arm, and 98 were randomised to the control arm. Of the 98 patients randomised to the control arm, 73 were stratified to cabozantinib, and 25 were stratified to vandetanib. 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. 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. Efficacy results for the ITT population are summarized in Table 9 and Figure 2.

Table 9 LIBRETTO-531: Summary of efficacy data (BICR assessment, ITT population)

	Selpercatinib	**Control (Cabozantinib or Vandetanib)**
Progression-free survival	**N = 193**	**N = 98**
Median [months] (95% CI)	NE (NE, NE)	16.76 (12.22, 25.10)
Hazard ratio (95% CI)	0.280 (0.165, 0.475)	
Stratified log rank p-value	<0.0001	
30 months PFS rate (%) 95% CI	76.4 (66.5, 83.8)	24.8 (6.9, 48.3)
Treatment failure-free survival*	**N = 193**	**N=98**
Median [months] (95% CI)	NE (NE, NE)	13.93 (11.27, 25.10)
Hazard ratio (95% CI)	0.254 (0.153, 0.423)	
Stratified log rank p-value	<0.0001	
30 months TFFS rate (%) 95% CI	75.8 (65.9, 83.2)	25.3 (7.2, 48.8)
Objective response (CR + PR)		
% (95% CI)	69.4 (62.4, 75.8)	38.8 (29.1, 49.2)
Complete response n (%)	23 (11.9)	4 (4.1)
Partial response n (%)	111 (57.5)	34 (34.7)
Duration of response[#]		
Median [months] (95% CI)	NE (NE, NE)	16.56 (10.41, NE)
Rate (%) of patients with duration of response		
≥ 24 months (95% CI)	79.1 (66.9, 87.2)	NE (NE, NE)

CI = Confidence Interval, CR = complete response, NE = not estimable, PR = partial response
*Treatment failure-free survival is defined as the time from randomization to the first occurrence of: documented radiographic disease progression per RECIST 1.1, or unacceptable toxicity leading to treatment discontinuation as assessed by the investigator, or death due to any cause.
[#]Median duration of follow-up was 11.14 months (25^{th}, 75^{th} percentile: 5.62, 16.62) in the selpercatinib arm and 12.81 months (25^{th} and 75^{th} percentile: 6.34, 15.51) in the control arm. Data Cut-off date: 22 May 2023

Figure 2. LIBRETTO-531: Kaplan-Meier plot of progression-free survival (BICR assessment, ITT population)



Data cut off: 22 May 2023

At the time of the primary PFS analysis, 18 OS events were observed across the two arms. In the ITT population, the OS HR was 0.374 ([95% CI: 0.147, 0.949]). The censoring rate was 95.9% in the selpercatinib arm and 89.8% in the control arm.

Comparative tolerability was evaluated in 242 patients (selpercatinib arm, N=161; control arm, N=81). The selpercatinib arm had a statistically significantly lower proportion of time on treatment where patients reported “high side effect bother” (8%) than the control arm (24%) (95% CI: -23%, -10%, p<0.0001) as assessed by Functional Assessment of Cancer Therapy item GP5 response 3 “Quite a bit” or 4 “Very much”.

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.

LIBRETTO-001

Of the 324 *RET*-mutant MTC patients enrolled in LIBRETTO-001, 143 were naïve to treatment with cabozantinib and vandetanib. Of these 116 were treatment naïve to other systemic therapy and 27 had previously received other systemic therapy. Among patients naïve to cabozantinib and vandetanib, the median age was 57 years (range 15 to 87 years). 2 patients (1.4%) were < 18 years of age. 58.0% of patients were male. 86.7% of patients were White, 5.6% were Asian, 1.4% were Black. Most patients (97.9%) had metastatic disease at enrolment. ECOG performance status was reported as 0-1 (95.9%) or 2 (4.2%). The most common mutation was M918T (60.1%), followed by extracellular cysteine mutations (23.8%). Efficacy results for cabozantinib and vandetanib treatment-naive *RET*-mutant MTC patients are summarised in Table 10.

Table 10 LIBRETTO-001: Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	143
Objective response (CR + PR)	
% (95% CI)	82.5 (75.3, 88.4)
Complete response n (%)	34 (23.8)
Partial response n (%)	84 (58.7)
Duration of response (months)*	
Median, 95% CI	NE (51.3, NE)
Rate (%) of duration of response	
≥ 12 months (95% CI)	91.4 (84.6, 95.3)
≥ 24 months (95% CI)	84.1 (75.9, 89.7)

CI = Confidence Interval, CR = complete response, NE = not estimable, PR = partial response
*Median duration of follow-up was 39.4 months (25^{th}, 75^{th} percentile: 32.3, 45.4).
Data cut-off date 13 January 2023

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 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. The most common mutation was M918T (65.1%), followed by extracellular cysteine mutations (15.8%). 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. Efficacy results for previously treated RET-mutant MTC are summarised in Table 11.

Table 11 LIBRETTO-001: Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	152
Objective response (CR + PR)	
% (95% CI)	77.6 (70.2, 84.0)
Complete response n (%)	19 (12.5)
Partial response n (%)	99 (65.1)
Duration of response (months)*	
Median (95% CI)	45.3 (33.6, NE)
Rate (%) of duration of response	
≥ 12 months (95% CI)	83.0 (74.6, 88.8)
≥ 24 months (95% CI)	66.4 (56.3, 74.7)

CI = Confidence Interval, CR = complete response, NE = not estimable, PR = partial response
*Median duration of follow-up was 38.3 months (25^{th}, 75^{th} percentile: 23.0, 46.1).
Data cut-off date 13 January 2023

Paediatric population

As of 13 January 2023, 10 patients with *RET* fusion-positive thyroid cancer aged 12 to ≤ 21 years have been treated in LIBRETTO-121, an ongoing Phase 1/2 study in

paediatric patients with an advanced solid or primary CNS tumour harbouring an activating RET alteration. Of these 10 patients, 8 patients were less than 18 years of age. Of the 10 patients, 4 were previously treated with radioactive iodine only, 2 had received prior systemic therapy that did not include radioactive iodine and 4 were not previously treated with any systemic therapy. For all 10 patients, per IRC, objective response rate was 60.0% (95% CI: 26.2, 87.8). 3 patients had confirmed complete response whilst 3 patients had confirmed partial response.

The Medicines and Healthcare Regulatory Agency has waived the obligation to submit the results of studies with selpercatinib in patients aged 6 months and below in solid tumours (see section 4.2 for information on paediatric use).

The licensing authority has deferred the obligation to submit the results of studies with selpercatinib in one or more subsets of the paediatric population in relapsed/refractory solid tumours, including RET fusion-positive solid tumours, RET-mutant medullary thyroid cancer, and other tumours with RET alteration/activation (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The licensing authority will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of selpercatinib were evaluated in patients with locally advanced or metastatic solid tumours administered 160 mg twice daily unless otherwise specified. Steady-state selpercatinib AUC and C_{max} increased in a linear to supra-dose proportional manner over the dose range of 20 mg once daily to 240 mg twice daily.

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

In vivo studies indicate that selpercatinib is a mild inhibitor of P-gp.

In vitro studies indicate that selpercatinib does not inhibit or induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. *In vitro* studies indicate that selpercatinib inhibits MATE1, and BCRP, but does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, and MATE2-K at clinically relevant concentrations. Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1.

The hard capsule and film-coated tablet dosage forms of selpercatinib are bioequivalent.

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 73.2% (range: 60.2-81.5%).

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), estimated by Population PK analysis, is 203.1 (69%) L following oral administration of selpercatinib in adult patients. Selpercatinib is 96% bound to human plasma proteins *in vitro* and binding is independent of concentration. The blood-to-plasma concentration ratio is 0.7.

Biotransformation

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 5.5 (45%) L/h and the half-life is 26.5 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.

Special populations

Age, gender and body weight
Age (range: 12 years to 92 years) or gender had no clinically meaningful effect on the pharmacokinetics of Retsevmo. Patients with a body weight < 50 kg should start Retsevmo treatment with a dose of 120 mg twice daily, while patients ≥ 50 kg should start Retsevmo treatment with a dose of 160 mg twice daily.

Hepatic impairment
Selpercatinib $AUC_{0-\infty}$ increased by 7% in subjects with mild, 32% in subjects with moderate Child-Pugh classification. Thus, selpercatinib exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh class A and B) is comparable to exposure in healthy subjects when a dose of 160 mg is administered. Selpercatinib $AUC_{0-\infty}$ increased by 77% in subjects with severe hepatic impairment (Child-Pugh class C). There is limited clinical data on the safety of selpercatinib in patients with severe hepatic impairment. Therefore, dose modification is recommended for patients with severe hepatic impairment (section 4.2).

Renal impairment
In a clinical pharmacology study using single dose selpercatinib 160 mg, exposure (AUC) was unchanged in subjects with mild, moderate, or severe renal impairment.

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

Paediatric population
Based on limited pharmacokinetic data, the C_{max} and AUC was similar in adolescent patients, 12-18 years of age, and in adults.

5.3 Preclinical safety data

Repeat-dose studies were conducted in juvenile and adolescent/adult rats and adolescent/adult minipigs to characterize toxicity. Target organs of toxicity common to the rat and minipig were hematopoietic system, lymphoid tissues, tongue, pancreas, gastro-intestinal tract, epiphyseal growth plate, and male reproductive tissues. In general, toxicities in these organs were reversible; the exceptions were the testicular toxicity in adolescent/adult and juvenile animals, and changes in growth plates in juvenile rats. Reversible toxicity was observed in the ovaries 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 only occurring in these organs in rats were reversible.

Juvenile toxicity

Selpercatinib exposure approximately 0.5-2 times the exposure in adult humans caused mortality in rats younger than 21 days old. Comparable exposure was tolerated in rats aged 21 days and older.

Juvenile and adolescent/adult rats and adolescent/adult minipigs with open growth plates administered selpercatinib exhibited microscopic changes of hypertrophy, hyperplasia, and dysplasia of growth plate cartilage (physis). In juvenile rats, the dysplasia at the growth plates was irreversible and associated with decreased femur length and reductions in bone mineral density. Skeletal changes were observed at exposure levels equivalent to those seen in adult patients taking the recommended dose of 160 mg BID.

Juvenile male rats administered selpercatinib and allowed to reach reproductive age after cessation of administration, exhibited decreased reproductive performance when mated with untreated female rats. Decreased fertility and copulation indices, increased pre- and post-implantation losses, and decreased number of viable embryos, were observed at an exposure approximately 3.4 times the efficacious exposure in adults.

Genotoxicity

Selpercatinib is not genotoxic at therapeutic doses. In an *in vivo* micronucleus assay in rats, selpercatinib was positive at concentrations >7 times the C_{max} at the human dose of 160 mg twice daily. In an *in vitro* micronucleus assay in human peripheral blood lymphocytes, an equivocal response was observed at a concentration approximately 485 times the C_{max} at the human dose.

Mutagenesis

Selpercatinib did not cause mutations in a bacterial mutagenicity assay.

Carcinogenesis

In a 2-year carcinogenicity study of selpercatinib in rats, vaginal tumours 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.

Embryotoxicitiy / Teratogenicity

Based on data from animal reproduction studies and its mechanism of action, selpercatinib can cause foetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations.

Reproduction toxicity

Results of studies conducted in rats and minipigs suggest that selpercatinib could impair fertility in males and females.
In a fertility study in male rats, dose-dependent germ cell depletion and spermatid retention were observed at subclinical AUC-based exposure levels (0.2 times the clinical exposure at the recommended human dose). These effects were associated with reduced organ weights, reduced sperm motility, and an increase in the number of abnormal sperm at AUC-based exposure levels approximately twice 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 subclinical 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, a reduction in the number of estrous cycles as well as embryolethality were observed at AUC-based exposure levels approximately equal to clinical exposure at the recommended human dose. In repeat-dose studies in rats, reversible vaginal mucification with individual cell cornification and altered estrous cycles were noted at clinically relevant AUC-based exposure levels. In minipigs, decreased corpora lutea and/or corpora luteal cysts were observed at subclinical AUC-based clinical exposure levels (0.07 to 0.3 times the clinical exposure at the recommended human dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline
Mannitol
Croscarmellose sodium
Hydroxypropylcellulose
Sodium stearyl fumarate

Film-coating

Retsevmo 40 mg film-coated tablets
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Black iron oxide (E172)

Retsevmo 80 mg film-coated tablets
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Red iron oxide (E172)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Cold formable aluminium foil (CFAF) blisters sealed with aluminium foil lidding. Each pack contains 30, 56 or 60 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000,
3528 BD Utrecht,
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PL 14895/0358

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 February 2021
Date of latest renewal: 12 March 2026

10 DATE OF REVISION OF THE TEXT

22/04/2026