▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – RETEVMO® (SELPERCATINIB) TABLET

1 NAME OF THE MEDICINE

Selpercatinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RETEVMO 40 mg immediate release film-coated tablets

Each immediate release film-coated tablet contains 40 mg selpercatinib

RETEVMO 80 mg immediate release film-coated tablets

Each immediate release film-coated tablet contains 80 mg selpercatinib

RETEVMO 120 mg immediate release film-coated tablets

Each immediate release film-coated tablet contains 120 mg selpercatinib

RETEVMO 160 mg immediate release film-coated tablets

Each immediate release film-coated tablet contains 160 mg selpercatinib

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

RETEVMO 40 mg immediate release film-coated tablets

Light grey, round tablet debossed on one side with “5340” and debossed with “Ret 40” on the other side. The diameter of the tablet is approximately 6 mm.

RETEVMO 80 mg immediate release film-coated tablets

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

RETEVMO 120 mg immediate release film-coated tablets

Light purple, round tablet debossed on one side with “6120” and debossed with “Ret 120” on the other. The diameter of the tablet is approximately 8.75 mm.

RETEVMO 160 mg immediate release film-coated tablets

Light pink, round tablet debossed on one side with “5562” and debossed with “Ret 160” on the other. The diameter of the tablet is approximately 9.75 mm.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RETEVMO is indicated for the treatment of adult patients with locally advanced or metastatic *RET* fusion positive non-small cell lung cancer (NSCLC).

RETEVMO is indicated for the treatment of adult and adolescent (12 years of age and older) patients with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Dose

The recommended dose of RETEVMO 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.

Avoid concomitant use of strong CYP inhibitors (see Section 4.5 Interactions with other medicines and other forms of interactions). If coadministration with strong CYP3A inhibitor cannot be avoided, reduce the current selpercatinib dose by 50%. If the CYP3A inhibitor is discontinued, increase the selpercatinib dose (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. Generally, dose reductions should be in 40 mg decrements. RETEVMO dose modifications are summarised in Table 1 and Table 2.

Table 1 Recommended dose modifications for RETEVMO for adverse reactions based in body weight

Dose modification	Body weight ≥50 kg	Body weight <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 reactions (ADR)	Grade	Dose modifications
Increased ALT or AST	Grade 3 or Grade 4	• Suspend dose until toxicity resolves to baseline (see sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)). 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 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)). 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 Special warnings and precautions for use). • 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.

Adverse drug reactions (ADR)	Grade	Dose modifications
		• 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 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)).
	Grade 4	• Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled.
Haemorrhagic events	Grade 3 or Grade 4	• Selpercatinib should be suspended until recovery to baseline. • Discontinue selpercatinib for severe or life-threatening haemorrhagic events.
Interstitial lung disease/Pneumonitis	Grade 2 that is persistent or recurs	• If persistent or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days, suspend selpercatinib until toxicity resolves to baseline or Grade 1. Dosing should be resumed at the next lower dose.
	Grade 3 or Grade 4	• Discontinue selpercatinib.
Hypothyroidism	Grade 3 or Grade 4	• Selpercatinib should be suspended until resolution to Grade 1 or baseline. • Discontinue selpercatinib based on severity.
Other adverse reactions	Grade 3 or Grade 4	• Selpercatinib should be suspended until recovery to baseline. • Discontinue selpercatinib for severe or life-threatening events.

Special populations

Elderly

No dose adjustment is required based on age (see section 5.2 Pharmacokinetic properties).

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 Pharmacokinetic properties).

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 Pharmacokinetic properties).

Paediatric population

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

RETEVMO should not be used in children aged less than 12 years. RETEVMO is intended to be used from the age of 12 years for the treatment of patients with *RET*-mutant MTC (see section 5.1 Pharmacodynamic properties, Clinical trials). Patients should be dosed according to body weight (see section 4.2 Dose and method of administration). Based on results from a preclinical study (see section 5.3 Preclinical safety data, Juvenile animal toxicity data), 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

RETEVMO is for oral administration.

The tablets should be swallowed whole (patients should not crush, chew or split the tablet before swallowing) and can be taken with or without food.

Patients should take the doses at approximately the same time every day.

RETEVMO concomitant use with strong CYP inducers should be avoided (see section 4.5 Interactions with other medicines and other forms of interactions).

RETEVMO must be accompanied by a meal if used concomitantly with a proton pump inhibitor (see section 4.5 Interactions with other medicines and other forms of interactions).

RETEVMO should be administered 2 hours before or 10 hours after concomitant H_2 receptor antagonists (see section 4.5 Interactions with other medicines and other forms of interactions).

Locally acting antacids should be administered 2 hours before or 2 hours after RETEVMO.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Interstitial lung disease/Pneumonitis

Interstitial lung disease (ILD) and/or pneumonitis, including severe and life-threatening disease, was reported in patients receiving selpercatinib (see section 4.8 Adverse effects (Undesirable effects)). Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and treat as medically appropriate. Based on the severity of ILD/pneumonitis, selpercatinib may require dose interruption or discontinuation (see section 4.2 Dose and method of administration).

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 Adverse effects (Undesirable effects)). 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 Dose and method of administration).

Hypertension

Hypertension was reported in patients receiving selpercatinib (see section 4.8 Adverse effects (Undesirable effects)). 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 Dose and method of administration). 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 Pharmacodynamic properties). 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 (see section 4.5 Interactions with other medicines and other forms of interactions).

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 medications known to prolong the QT interval.

Selpercatinib may require dose interruption or modification (see section 4.2 Dose and method of administration).

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 Interactions with other medicines and other forms of interactions).

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, pregnancy and lactation).

Fertility

Based on nonclinical safety findings, male and female fertility may be compromised by treatment with RETEVMO (see sections 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data). 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 Adverse effects (Undesirable effects)). 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 Dose and method of administration). 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 Adverse effects (Undesirable effects)).

Permanently discontinue selpercatinib in patients with severe or life-threatening haemorrhage (see section 4.2 Dose and method of administration).

Hypothyroidism

Selpercatinib can cause hypothyroidism. Hypothyroidism occurred in 16.1% (135/837) of patients with other solid tumours including NSCLC; all reactions were Grade 1 or 2.

Monitor thyroid function before treatment with RETEVMO and periodically during treatment. Treat with thyroid hormone replacement as clinically indicated, 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. Withhold RETEVMO until clinically stable or permanently discontinue RETEVMO based on severity (see section 4.2 Dose and method of administration).

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, RETEVMO has the potential to adversely affect wound healing.

Withhold RETEVMO 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 RETEVMO after resolution of wound healing complications has not been established.

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.

Slipped Capital Femoral Epiphysis (SCFE)/ Slipped Upper Femoral Epiphysis (SUFE) in Adolescent Patients

SCFE/SUFE has been reported in adolescent patients receiving selpercatinib (see section 4.8 Adverse effects (Undesirable effects)). Patients should be monitored for symptoms indicative of SCFE/SUFE and treated as medically and surgically appropriate.

Use in the elderly

No dose adjustment is required based on age (see section 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties). 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.

Paediatric use

The safety of selpercatinib in children aged less than 18 years with *RET* fusion-positive NSCLC has not been established.

The safety of selpercatinib in children aged less than 12 years with *RET*-mutant MTC has not been established.

SCFE/SUFE has been reported in adolescent patients receiving selpercatinib (see section 4.4, Slipped Capital Femoral Epiphysis (SCFE)/ Slipped Upper Femoral Epiphysis (SUFE) in Adolescent Patients). Based on results from a preclinical study (see section 5.3 Preclinical safety data Juvenile animal toxicity data), 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.

Effects on laboratory tests

Hepatic transaminases should be monitored prior to the start of selpercatinib therapy, at every 2 weeks interval during the first 3 months, monthly for the next 3 months and as clinically indicated.

Serum electrolytes should be monitored in all patients after 1 week of selpercatinib treatment, at least monthly for the first 6 months and as clinically indicated (see Sections 4.4 Special warnings and precautions for use and 4.2 Dose and method of administration).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

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 CYP3A4 inhibitor, increased the C_{max} and AUC of selpercatinib by 30% and 130%, respectively, compared to selpercatinib given alone, which may increase the risk of an ADR, including QTc prolongation. 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 Dose and method of administration and section 4.4 Special warnings and precautions for use; QT interval prolongation).

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.

Coadministration 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.

Coadministration 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 RETEVMO was administered with food.

Co-administration with medicinal products that are substrates of transporters

In vitro studies indicate that selpercatinib inhibits MATE1, P-gp, and BCRP, but does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, and MATE2-K at clinically relevant concentrations. *In vivo* interactions of selpercatinib with clinically relevant substrates of MATE1, such as creatinine, may occur.

In vivo, selpercatinib increased C_{max} 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).

Paediatric population

Interaction studies have only been performed in adults.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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 RETEVMO (see 4.6 Fertility, pregnancy and lactation, *Reproduction toxicity*). Both male and female patients (including adolescent patients) should seek advice on fertility preservation before treatment.

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

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. These effects were associated with reduced organ weights, reduced sperm motility, and an increase in the number of abnormal sperm exposures 2-fold the human exposure based on AUC at the maximum 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.

In a fertility and early embryonic study in female rats, a reduction in the number of oestrus cycles as well as embryolethality were observed at AUC-based exposure levels approximately equal to clinical exposure at the maximum recommended human dose. In repeat-dose studies in rats, reversible vaginal mucification with individual cell cornification and altered oestrus 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.

Use in pregnancy – Pregnancy Category D

There are no available data from the use of selpercatinib in pregnant women. Studies in animals have shown reproductive toxicity. RETEVMO 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.

Embryotoxicity/Teratogenicity

Based on data from animal reproduction studies and its mechanism of action, selpercatinib can cause fetal harm when administered to a pregnant woman. In an embryo-fetal development study, once daily oral administration of selpercatinib at a dose level of 50 mg/kg (approximately 1.4 times the human exposure based on AUC at the clinical dose of 160 mg twice daily) to pregnant rats during the period of organogenesis resulted in mean 96.4% post-implantation loss per litter and an increase in external malformations.

Use in lactation

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 RETEVMO and for at least one week after the last dose.

4.7 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.

RETEVMO 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 RETEVMO (see section 4.8 Adverse effects (Undesirable effects)).

4.8 ADVERSE EFFECTS (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.

Median time on treatment with selpercatinib was 30.1 months with mean (standard deviation) for relative dose intensity 83.4% (19.6) (Study LIBRETTO-001), 16.7 months (Study LIBRETTO-431) and 14.9 months (Study LIBRETTO-531).

The most common serious adverse events (SAE) occurring in ≥1% were 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%), AST increased (1.0%).

Permanent discontinuation of RETEVMO 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%), hypersensitivity (0.3%), haemorrhage (0.3%) and thrombocytopenia (0.3%).

Tabulated list of adverse drug reactions

The integrated frequency and severity of ADRs reported in the 1188 patients treated with selpercatinib are shown in Table 3, of these 520 patients had *RET* fusion positive NSCLC and 517 patients had *RET*-mutant MTC.

The ADRs are classified according to MedDRA the system 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).

Table 3 Treatment-Emergent adverse drug reactions in patients receiving selpercatinib

System organ class	Selpercatinib (N=1188)	
	Frequency of all Grades n (%)[a]	Frequency of Grade ≥3 toxicity n (%)[a]
Infections and infestations		
Pneumonia[b]	128 (10.8)	65 (5.5)

System organ class	Selpercatinib (N=1188)	
	Frequency of all Grades n (%)[a]	Frequency of Grade ≥3 toxicity n (%)[a]
Urinary tract infections[b]	203 (17.1)	22 (1.9)
Immune system disorders		
Hypersensitivity[bc]	52 (4.4)	18 (1.5)
Endocrine disorders		
Hypothyroidism[b]	178 (15.0)	0
Metabolism and nutrition disorders		
Decreased appetite	235 (19.8)	8 (0.7)
Nervous system disorders		
Headache[b]	312 (26.3)	16 (1.3)
Dizziness[b]	206 (17.3)	4 (0.3)
Cardiac disorders		
Electrocardiogram QT prolonged[b]	235 (19.8)	64 (5.4)
Vascular disorders		
Hypertension[b]	519 (43.7)	236 (19.9)
Gastrointestinal disorders		
Abdominal pain[b]	381 (32.1)	28 (2.4)
Diarrhoea[b]	544 (45.8)	57 (4.8)
Nausea	329 (27.7)	16 (1.3)
Vomiting[b]	261 (22.0)	20 (1.7)
Constipation	360 (30.3)	7 (0.6)
Dry mouth[b]	490 (41.2)	1 (0.1)
Stomatitis[b]	201 (16.9)	4 (0.3)
Chylous ascites[b]	19 (1.6)	4 (0.3)
Skin and subcutaneous tissue disorders		
Rash[b]	403 (33.9)	12 (1.0)
General disorders and administration site conditions		
Pyrexia	202 (17.0)	5 (0.4)
Fatigue[b]	512 (43.1)	46 (3.9)
Oedema[b]	561 (47.2)	13 (1.1)
Investigations[d]		
ALT increased	697 (59.4)	165 (14.1)
AST increased	718 (61.0)	112 (9.5)
Calcium decreased	692 (58.8)	75 (6.4)
Lymphocyte count decreased	604 (52.5)	222 (19.3)
Albumin decreased	556 (47.2)	31 (2.6)
White blood cell count decreased	585 (49.6)	30 (2.5)
Creatinine increased	511 (43.4)	41 (3.5)
Sodium decreased	480 (40.8)	118 (10.0)
Platelets decreased	470 (39.9)	39 (3.3)
Alkaline Phosphatase Increased	478 (40.6)	49 (4.2)
Total Bilirubin Increased	398 (33.8)	28 (2.4)
Magnesium decreased	342 (29.2)	12 (1.0)
Haemoglobin decreased	349 (29.6)	37 (3.1)
Neutrophil count decreased	360 (31.1)	59 (5.1)
Potassium decreased	222 (18.9)	23 (2.0)
Blood and lymphatic system		
Haemorrhage[b]	242 (20.4)	30 (2.5)
Respiratory, thoracic and mediastinal disorders		
Chylothorax	19 (1.6)	5 (0.4)
ILD/Pneumonitis[b]	31 (2.6)	5 (0.4)

a. Very common = ≥10%, Common = ≥1% and < 10%, Uncommon = ≥0.1% and <1%

b. Consolidated term
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. Based on laboratory assessments.

LIBRETTO-001

The safety data from study LIBRETTO-001 is based mainly on an adult population who were treated with selpercatinib for solid tumours, which includes participants with non-small cell lung cancer, thyroid cancer, and medullary thyroid cancer.

The most common serious adverse events (SAE) occurring in ≥2% of the overall LIBRETTO-001 safety population were pneumonia (6.6%), dyspnoea (3.1%), pleural effusion (3.0%), hyponatraemia (2.7%), abdominal pain (2.6%), sepsis (2.3%) and diarrhoea (2.0%). Hypersensitivity occurred in 3.9% of patients with *RET* fusion positive NSCLC but was below 2% incidence for the overall safety population.

Permanent discontinuation of RETEVMO for treatment emergent adverse events, regardless of attribution occurred in 9.6% of patients.

Tabulated list of adverse drug reactions

Treatment emergent adverse events (TEAE) occurring in >10% in patients receiving single agent selpercatinib (LIBRETTO-001) are shown in Table 4.

Table 4 Treatment-Emergent Adverse Events (>10%) in Patients Receiving Single Agent Selpercatinib (LIBRETTO-001)

Preferred Term	**Selpercatinib (N=837)**	
	Frequency of All Grades n (%)	**Frequency of Grade ≥ 3 n (%)**
Diarrhoea	419 (50.1)	49 (5.9)
Dry mouth	366 (43.7)	0
Hypertension	353 (42.2)	165 (19.7)
Fatigue	332 (39.7)	22 (2.6)
Aspartate aminotransferase increased	316 (37.8)	73 (8.7)
Alanine aminotransferase increased	305 (36.4)	99 (11.8)
Oedema peripheral	303 (36.2)	5 (0.6)
Constipation	295 (35.2)	7 (0.8)
Nausea	289 (34.5)	14 (1.7)
Headache	245 (29.3)	15 (1.8)
Abdominal pain	237 (28.3)	25 (3.0)
Blood creatinine increased	226 (27.0)	6 (0.7)
Vomiting	226 (27.0)	20 (2.4)
Cough	194 (23.2)	0
Rash	193 (23.1)	3 (0.4)
Arthralgia	192 (22.9)	3 (0.4)
Dyspnoea	190 (22.7)	33 (3.9)
Back pain	187 (22.3)	17 (2.0)
Decreased appetite	185 (22.1)	7 (0.8)
Electrocardiogram QT prolonged	175 (20.9)	41 (4.9)

Preferred Term	Selpercatinib (N=837)	
	Frequency of All Grades n (%)	Frequency of Grade ≥ 3 n (%)
Pyrexia	158 (18.9)	2 (0.2)
Urinary tract infection	155 (18.5)	15 (1.8)
Dizziness	148 (17.7)	2 (0.2)
Thrombocytopenia	145 (17.3)	29 (3.5)
Hypocalcaemia	142 (17.0)	24 (2.9)
Hyponatraemia	139 (16.6)	77 (9.2)
Insomnia	137 (16.4)	0
Dry skin	136 (16.2)	0
Blood alkaline phosphatase increased	128 (15.3)	21 (2.5)
Leukopenia	126 (15.1)	13 (1.6)
Ascites	124 (14.8)	17 (2.0)
Lymphopenia	122 (14.6)	49 (5.9)
Hypoalbuminaemia	121 (14.5)	9 (1.1)
Gastrooesophageal reflux disease	120 (14.3)	3 (0.4)
Abdominal distension	119 (14.2)	2 (0.2)
Anaemia	119 (14.2)	28 (3.3)
Corona virus infection	118 (14.1)	9 (1.1)
Pleural effusion	118 (14.1)	22 (2.6)
Hypomagnesaemia	117 (14.0)	3 (0.4)
Pain in extremity	114 (13.6)	3 (0.4)
Myalgia	111 (13.3)	3 (0.4)
Stomatitis	108 (12.9)	2 (0.2)
Hyperkalaemia	107 (12.8)	17 (2.0)
Upper respiratory tract infection	102 (12.2)	4 (0.5)
Blood bilirubin increased	100 (11.9)	13 (1.6)
Weight increased	98 (11.7)	19 (2.3)
Dysphonia	96 (11.5)	1 (0.1)
Neutropenia	96 (11.5)	22 (2.6)
Asthenia	94 (11.2)	11 (1.3)
Weight decreased	94 (11.2)	6 (0.7)
Face oedema	92 (11.0)	1 (0.1)
Rash maculo-papular	92 (11.0)	3 (0.4)
Hypokalaemia	90 (10.8)	17 (2.0)
Hypothyroidism	90 (10.8)	0
Hyperphosphataemia	89 (10.6)	0
Alopecia	87 (10.4)	0
Musculoskeletal pain	87 (10.4)	1 (0.1)

Abbreviations: n = number of patients with TEAEs; N = number of patients in the population; TEAE = treatment emergent adverse event.
Patients are counted once within each preferred term.

The ADRs reported in the 837 patients treated with selpercatinib are shown in Table 5, of these 362 patients had *RET* fusion positive NSCLC.

Table 5 Adverse drug reactions (>1.0%) in patients receiving single agent selpercatinib (LIBRETTO-001)

System Organ Class Event	Selpercatinib (N=837)	
	Frequency of All Grades n (%)	**Frequency of Grade ≥ 3 n (%)**
Endocrine disorders		
Hypothyroidism[a]	136 (16.2)	N/A
Gastrointestinal disorders		
Dry mouth[b]	366 (43.7)	N/A
Diarrhoea[b]	423 (50.5)	49 (5.9)
Constipation	295 (35.2)	7 (0.8)
Nausea	289 (34.5)	14 (1.7)
Abdominal pain[b]	306 (36.6)	26 (3.1)
Vomiting[b]	226 (27.0)	20 (2.4)
Chylous ascites[b]	16 (1.9)	2 (0.2)
General Disorders and Administration site Conditions		
Fatigue[b]	407 (48.6)	33 (3.9)
Oedema[b]	433 (51.7)	9 (1.1)
Pyrexia	158 (18.9)	2 (0.2)
Immune system disorders		
Hypersensitivity[bc]	48 (5.7)	16 (1.9)
Infections and infestations		
Pneumonia[d]	110 (13.1)	57 (6.8)
Investigations		
Electrocardiogram QT prolonged[b]	177 (21.1)	41 (4.9)
Metabolism and nutrition disorders		
Decreased appetite	185 (22.1)	7 (0.8)
Nervous system disorders		
Headache[b]	246 (29.4)	15 (1.8)
Dizziness[b]	178 (21.3)	3 (0.4)
Respiratory, thoracic and mediastinal disorders		
Chylothorax	18 (2.2)	5 (0.6)
ILD/Pneumonitis[a]	22 (2.6)	4 (0.5)
Skin and subcutaneous tissue disorders		
Rash[b]	315 (37.6)	6 (0.7)
Vascular disorders		
Hypertension[b]	360 (43.0)	167 (20.0)
Haemorrhage[f]	203 (24.3)	29 (3.5)
Laboratory Parameters[e]		
AST increased	511 (61.3)	87 (10.4)
ALT increased	473 (56.7)	102 (12.2)
Alkaline phosphatase increased	355 (42.6)	36 (4.3)
Total bilirubin increased	257 (30.8)	24 (2.9)
Blood creatinine increased	425 (51.0)	30 (3.6)
Platelets decreased	336 (40.3)	32 (3.8)
Magnesium decreased	300 (36.1)	5 (0.6)
Lymphocyte count decreased	444 (55.1)	174 (21.6)

System Organ Class Event	Selpercatinib (N=837)	
	Frequency of All Grades n (%)	Frequency of Grade ≥ 3 n (%)
Haemoglobin decreased	282 (33.8)	33 (4.0)
White blood cell count decreased	423 (50.7)	24 (2.9)
Neutrophil count decreased	215 (26.4)	29 (3.6)

Abbreviations: FMQ = FDA Medical Query; LLT = lowest level term; MedRA = Medical Dictionary for Regulatory Activities; n = number of patients who experienced ADRs; N = total population; N/A=not applicable.

[a] As defined by narrow and broad standardised MedDRA Query (SMQ)

[b] Lilly-defined cluster:

Dry mouth: dry mouth, mucosal dryness

Diarrhoea: diarrhoea, anal incontinence, defecation urgency, frequent bowel movements, gastrointestinal hypermotility

Abdominal pain: abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, gastrointestinal pain

Vomiting: vomiting, retching, regurgitation

Chylous ascites: chylous ascites, ascites chylous (MedDRA LLTs)

Fatigue: fatigue, asthenia, malaise

Oedema: oedema peripheral, face oedema, periorbital oedema, swelling face, peripheral swelling, localised oedema, eyelid oedema, generalised oedema, eye swelling, lymphoedema, orbital oedema, eye oedema, oedema, oedema genital, swelling, scrotal oedema, scrotal swelling, angioedema, skin oedema, testicular swelling, vulvovaginal swelling

Hypersensitivity: drug hypersensitivity, hypersensitivity

Electrocardiogram PT prolongation: Electrocardiogram QT prolonged, Electrocardiogram QT interval abnormal

Headache: headache, sinus headache, tension headache

Dizziness: dizziness, vertigo, presyncope, dizziness postural

Rash: rash, rash maculo-papular, skin exfoliation, rash erythematous, rash macular, dermatitis, urticaria, rash pruritic, exfoliative rash, rash papular, dermatitis allergic, rash follicular, rash generalised, rash pustular, butterfly rash, rash morbilliform, rash vesicular

Hypertension: Hypertension, blood pressure increased.

[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] As defined by Narrow FDA Medical Query (FMQ)

[e] 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, which was 830 for magnesium decreased, 806 for lymphocyte count decreased, 814 for neutrophil count decreased and 834 for the others.

[f] 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, post-menopausal haemorrhage, retinal haemorrhage, scleral haemorrhage, subdural haemorrhage, traumatic haemothorax, tumour haemorrhage, upper gastrointestinal haemorrhage, uterine haemorrhage, and vessel puncture site haematoma.

LIBRETTO-431

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 (see Section 5.1 Clinical trials LIBRETTO-431). The most common SAE's occurring in ≥2% were pleural effusion (4.4%) and

abnormal hepatic function (2.5%). TEAE's occurring in ≥10% in patients receiving single agent selpercatinib (LIBRETTO-431) are shown in Table 6.

Permanent discontinuation for treatment emergent adverse events, regardless of attribution occurred in 10.1% of patients.

Table 6 TEAEs occurring in ≥10% in NSCLC patients receiving single agent selpercatinib (LIBRETTO-431)

Preferred Term	Selpercatinib (N=158)		Control (carboplatin or cisplatin + pemetrexed +/- pembrolizumab) (N=98)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Aspartate aminotransferase increased	97 (61.4)	20 (12.7)	39 (39.8)	1 (1.0)
Alanine aminotransferase increased	95 (60.1)	35 (22.2)	39 (39.8)	3 (3.1)
Hypertension	76 (48.1)	32 (20.3)	7 (7.1)	3 (3.1)
Diarrhoea	69 (43.7)	2 (1.3)	24 (24.5)	2 (2.0)
Dry mouth	61 (38.6)	0	6 (6.1)	0
Blood bilirubin increased	59 (37.3)	2 (1.3)	1 (1.0)	0
Oedema peripheral	41 (25.9)	3 (1.9)	13 (13.3)	0
Blood creatinine increased	36 (22.8)	0	15 (15.3)	1 (1.0)
Rash	35 (22.2)	1 (0.6)	21 (21.4)	0
Constipation	34 (21.5)	0	39 (39.8)	1 (1.0)
Electrocardiogram QT prolonged	32 (20.3)	14 (8.9)	1 (1.0)	0
Platelet count decreased	32 (20.3)	5 (3.2)	18 (18.4)	5 (5.1)
White blood cell count decreased	32 (20.3)	2 (1.3)	25 (25.5)	4 (4.1)
Neutrophil count decreased	31 (19.6)	3 (1.9)	25 (25.5)	12 (12.2)
COVID-19	30 (19.0)	1 (0.6)	18 (18.4)	0
Decreased appetite	27 (17.1)	0	33 (33.7)	2 (2.0)
Fatigue	24 (15.2)	2 (1.3)	26 (26.5)	1 (1.0)
Hypokalaemia	24 (15.2)	3 (1.9)	8 (8.2)	3 (3.1)
Hypoalbuminaemia	23 (14.6)	1 (0.6)	6 (6.1)	0
Weight increased	23 (14.6)	2 (1.3)	7 (7.1)	0
Headache	22 (13.9)	0	10 (10.2)	0
Pyrexia	21 (13.3)	1 (0.6)	23 (23.5)	0
Abdominal pain upper	20 (12.7)	0	13 (13.3)	0
Asthenia	20 (12.7)	1 (0.6)	25 (25.5)	4 (4.1)
Blood alkaline phosphatase increased	20 (12.7)	2 (1.3)	8 (8.2)	0
Gamma-glutamyltransferase increased	20 (12.7)	4 (2.5)	10 (10.2)	0
Nausea	20 (12.7)	0	43 (43.9)	1 (1.0)
Vomiting	20 (12.7)	0	23 (23.5)	1 (1.0)
Bilirubin conjugated increased	19 (12.0)	1 (0.6)	1 (1.0)	0
Stomatitis	19 (12.0)	0	9 (9.2)	0
Abdominal pain	18 (11.4)	1 (0.6)	7 (7.1)	2 (2.0)
Anaemia	18 (11.4)	2 (1.3)	57 (58.2)	10 (10.2)

Preferred Term	Selpercatinib (N=158)		Control (carboplatin or cisplatin + pemetrexed +/- pembrolizumab) (N=98)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Arthralgia	17 (10.8)	0	9 (9.2)	0
Cough	17 (10.8)	0	15 (15.3)	1 (1.0)
Pruritus	16 (10.1)	0	22 (22.4)	0

Abbreviations: COVID-19 = coronavirus disease 2019; N = number of patients in an analysis population; n = number of patients in specified category; TEAE = treatment-emergent adverse event.

LIBRETTO-531

TEAEs occurring in ≥10% in *RET*-mutant MTC patients receiving single agent selpercatinib (LIBRETTO-531) are shown in Table 7.

Table 7 TEAEs occurring in ≥10% in *RET*-mutant MTC patients receiving single agent selpercatinib (LIBRETTO-531)

Preferred Term	Selpercatinib (N=193)		Control (cabozantinib or vandetanib) (N=97)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Hypertension	82 (42.5)	36 (18.7)	40 (41.2)	17 (17.5)
Dry mouth	61 (31.6)	1 (0.5)	10 (10.3)	1 (1.0)
Alanine aminotransferase increased	51 (26.4)	20 (10.4)	33 (34.0)	2 (2.1)
Diarrhoea	51 (26.4)	6 (3.1)	59 (60.8)	8 (8.2)
Aspartate aminotransferase increased	46 (23.8)	9 (4.7)	37 (38.1)	2 (2.1)
Headache	44 (22.8)	1 (0.5)	20 (20.6)	0
Fatigue	36 (18.7)	7 (3.6)	21 (21.6)	5 (5.2)
Oedema peripheral	32 (16.6)	0	2 (2.1)	0
Constipation	31 (16.1)	0	12 (12.4)	0
Rash	28 (14.5)	2 (1.0)	20 (20.6)	2 (2.1)
Electrocardiogram QT prolonged	26 (13.5)	9 (4.7)	13 (13.4)	2 (2.1)
Decreased appetite	23 (11.9)	1 (0.5)	27 (27.8)	5 (5.2)
Pyrexia	23 (11.9)	2 (1.0)	2 (2.1)	0
Weight increased	22 (11.4)	3 (1.6)	2 (2.1)	0
Asthenia	21 (10.9)	1 (0.5)	24 (24.7)	4(4.1)
Blood bilirubin increased	21 (10.9)	1 (0.5)	8 (8.2)	1 (1.0)
COVID-19	20 (10.4)	1 (0.5)	17 (17.5)	0
Erectile dysfunction[a]	12 (10.4)	0	0	0
Hypocalcaemia	20 (10.4)	2 (1.0)	25 (25.8)	7 (7.2)
Nausea	20 (10.4)	2 (1.0)	31 (32.0)	5 (5.2)

Abbreviations: COVID-19 = coronavirus disease 2019; N = number of patients in an analysis population; n = number of patients in specified category; TEAE = treatment-emergent adverse event.
[a] Denominator adjusted because gender-specific event for males: N=115 (selpercatinib arm), N=67 (control arm).

Other Adverse Drug Reactions

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).

Description of selected adverse reactions

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 Dose and method of administration).

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 *Torsade de pointes*, events of Grade ≥3 or clinically significant treatment-emergent arrhythmias or ventricular tachycardia; one case of grade 3 ventricular fibrillation reported was felt to be unrelated to selpercatinib. Fatal events of sudden death and cardiac arrest were reported in patients, with no fatal events occurring due to ECG QT prolongation. Across all studies, two patients (0.2%) discontinued selpercatinib treatment due to QT prolongation.

RETEVMO may require dose interruption or modification (see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

Hypertension

Across all studies, 43.7% of patients experienced a hypertensive event of any grade, with 19.9% of patients experiencing events of Grade ≥3.

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 systolic 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% in LIBRETTO-001, 20.3% in LIBRETTO-431, and 19.2% in LIBRETTO-531 displayed treatment-emergent Grade ≥3 hypertension. Grade 4 treatment emergent hypertension was reported in 0.1% 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 Dose and method of administration). Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled with antihypertensive therapy (see section 4.4 Special warnings and precautions for use).

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 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.

RETEVMO may require dose interruption or modification (see section 4.2 Dose and method of administration).

Haemorrhages

Grade ≥3 haemorrhagic events occurred in 2.9% (29/995) 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 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 and 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 severe or life-threatening haemorrhage (see section 4.2 Dose and method of administration).

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 was 1 patient 12 years of age with *RET*-mutant MTC in LIBRETTO-531.

SCFE/SUFE has been commonly observed (6.4%) in patients <18 years of age treated with selpercatinib (n=47) (see section 4.4 Special warnings and precautions for use). Based on results from a preclinical study, open growth plates in adolescent patients should be monitored (see section 4.4 Special warnings and precautions for use, and section 5.3 Preclinical safety data, Juvenile animal toxicity data). No other unique safety findings in children aged less than 18 years have been identified.

Elderly

In patients receiving selpercatinib for solid tumours including NSCLC, thyroid cancer and medullary thyroid cancer, 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%), <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 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%) and ≥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%).

Post-marketing data

One case of fulminant hepatitis was reported in the post-marketing setting with peak AST of 4567 U/L (reference range 13-30 U/L) and peak ALT of 2801 U/L (reference range 7-23 U/L) approximately one month after commencing selpercatinib.

The following adverse drug reactions are based on post-marketing reports.

Skin and subcutaneous tissue disorders: Very rare (<0.01%): Stevens-Johnson Syndrome

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, protein kinase inhibitors.

ATC code: L01EX22

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 Dose and method of administration and 4.4 Special warnings and precautions for use).

Mechanism of action

Selpercatinib is an orally available, small molecule inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase. 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, promoting cell proliferation and survival in tumor cell lines. Point mutations in RET can also result in constitutively activated RET proteins that can promote cell growth and survival in tumor cell lines.

In RET enzyme assays, selpercatinib inhibits the kinase activity of RET, RET-V804L, RET-V804M, RET-A883F, RET-S904F, RET-A764T, RET-S891A and RET-M918T with IC50 values of 0.20 nM to 2.21 nM. In kinase screening assays, selpercatinib at a concentration of 100 nM inhibits only six of 329 non-RET kinases by more than 50% of the control. Among these, selpercatinib inhibits two kinases with IC50 values within 35-fold of RET: FLT4 (0.7-fold in an enzyme-based assay and 8-fold in a cell-based assay); and FLT1 (1.6-fold). Selpercatinib inhibits PDGFRB with an IC50 value of 2100 nM, and JAK1, JAK2, JAK3, TRKA, and TRKC with IC50 values greater than 5000 nM in enzyme assays.

Selpercatinib demonstrates *in vitro* inhibition of human cancer cell lines derived from multiple tumour types harbouring RET fusion genes and RET mutations with EC50 values equal to 10 nM or less. In *in vivo* mouse studies, selpercatinib demonstrates inhibition of tumor growth in RET fusion and RET mutant cancer cell lines, patient-derived RET fusion xenograft models, and a patient-derived RET fusion xenograft model harbouring a RET V804M mutation. Selpercatinib also exhibits intracranial anti-tumour activity of patient-derived RET fusion xenograft tumours implanted directly into the brain of mice.

In additional radioligand binding assays, selpercatinib inhibits two out of 54 non-kinase targets at a concentration of 1 μM: 5-HT transporter (70.2%) and α2c receptor (51.7%).

Clinical trials

Clinical efficacy and safety

The efficacy of RETEVMO was evaluated in adult patients with advanced RET fusion-positive NSCLC and in adult and adolescent patients with *RET*-mutant MTC in a phase 1/2, multi-centre, open-label, single-arm clinical study: Study LIBRETTO-001. Efficacy of RETEVMO in RET fusion-positive NSCLC and *RET*-mutant MTC was evaluated in the Phase 3 Studies, LIBRETTO-431 (see section *Treatment-naïve RET fusion-positive NSCLC*) and LIBRETTO-531 (see section *Vandetanib and cabozantinib naïve RET-mutant MTC*) respectively.

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 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 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 RETEVMO 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 hybridisation (FISH) and Nanostring technology. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (IRC) according to RECIST v1.1.

Treatment-naïve RET fusion-positive NSCLC

LIBRETTO-431

The efficacy of RETEVMO in RET fusion-positive NSCLC was evaluated 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/DCR by BICR, intracranial ORR/DOR by BICR, and time to deterioration in pulmonary symptoms by NSCLC-SAQ.

Of the 261 patients enrolled and randomised 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 or 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 8 and Figure 1.

Table 8 LIBRETTO-431: Summary of efficacy data (BICR assessment, ITT-Pembrolizumab population)

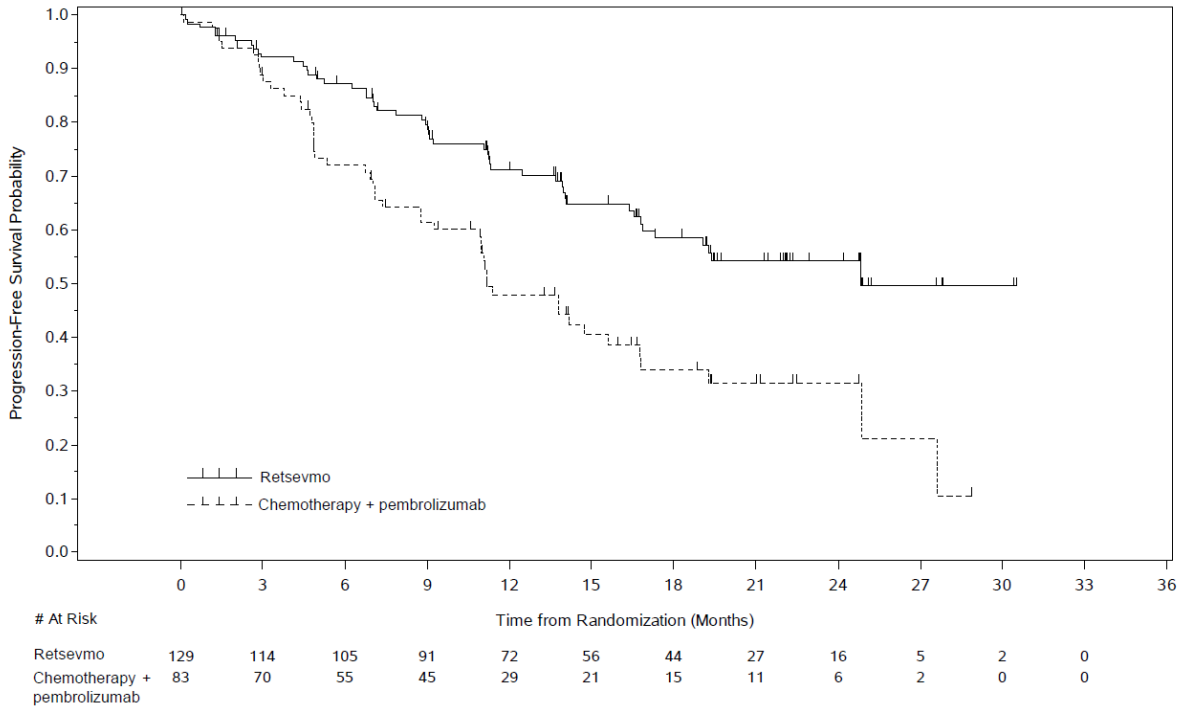
	Selpercatinib	**Control (platinum-based pemetrexed chemotherapy with pembrolizumab)**
Progression-free survival	**N = 129**	**N = 83**
BICR assessment, number of events (%)	49 (38.0)	49 (59.0)
Median [months] (95% CI)	24.84 (16.89, NE)	11.17 (8.77, 16.76)
Hazard ratio (95% CI)	0.465 (0.309, 0.699)	
Stratified 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*		
BICR assessment, number of events (%)	34 (31.5)	29 (53.7)
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)

NE = not estimable

*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)



OS was not mature at the time of the primary PFS analysis (40 events observed across the two arms). The censoring rate was 80.6% in the selpercatinib arm and 81.9% in the control arm and results may be confounded due to cross over. In the ITT-Pembrolizumab population the OS HR was 0.961 ([95% CI: 0.503, 1.835]; p=0.9033).

In the ITT-Pembrolizumab population, selpercatinib significantly delayed time to worsening of patient-reported NSCLC symptoms, as measured by the NSCLC-Symptom Assessment Questionnaire 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.

LIBRETTO-001

Of the 362 *RET* fusion-positive NSCLC patients enrolled in LIBRETTO-001, 69 were treatment naïve. Most patients (98.6%) had metastatic disease at enrolment. 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. 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-naïve *RET* fusion-positive NSCLC patients are summarised in Table 9.

Table 9 LIBRETTO-001: Key efficacy outcomes for treatment naive

	Efficacy by 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, n=57)	
Median, 95% CI	20.3 (15.4, 29.5)
Median duration of follow up	37.1
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)

Abbreviations: CI = confidence interval; CR = complete response; IRC = independent review committee; n = total number of patients who experienced complete or partial response; N = total number of subjects in the treatment naive population; PR = partial response.
Data cut-off date: 13 January 2023

Treatment-experienced RET fusion-positive NSCLC

A total of 247 patients had received prior platinum-based chemotherapy in study LIBRETTO-001. Most patients (97.2%) had metastatic disease at enrolment. 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. 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 10.

Table 10 LIBRETTO-001: Key efficacy outcomes for treatment experienced

	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, n=152)	
Median (95% CI)	31.6 (20.4, 42.3)
Median duration of follow-up (months)	39.5
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)

Abbreviations: CI = confidence interval; CR = complete response; IRC = independent review committee; n = total number of patients who experienced complete or partial response; N = total number of subjects in the platinum- experienced population; PR = partial response.
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 in patients with measurable disease 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 (range: 7.4, 15.3).

Vandetanib and cabozantinib naïve RET-mutant MTC

LIBRETTO-531

The efficacy of RETEVMO in *RET*-mutant MTC was confirmed in LIBRETTO-531, a phase 3 multicentre, 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 (aged ≥12 years) 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.

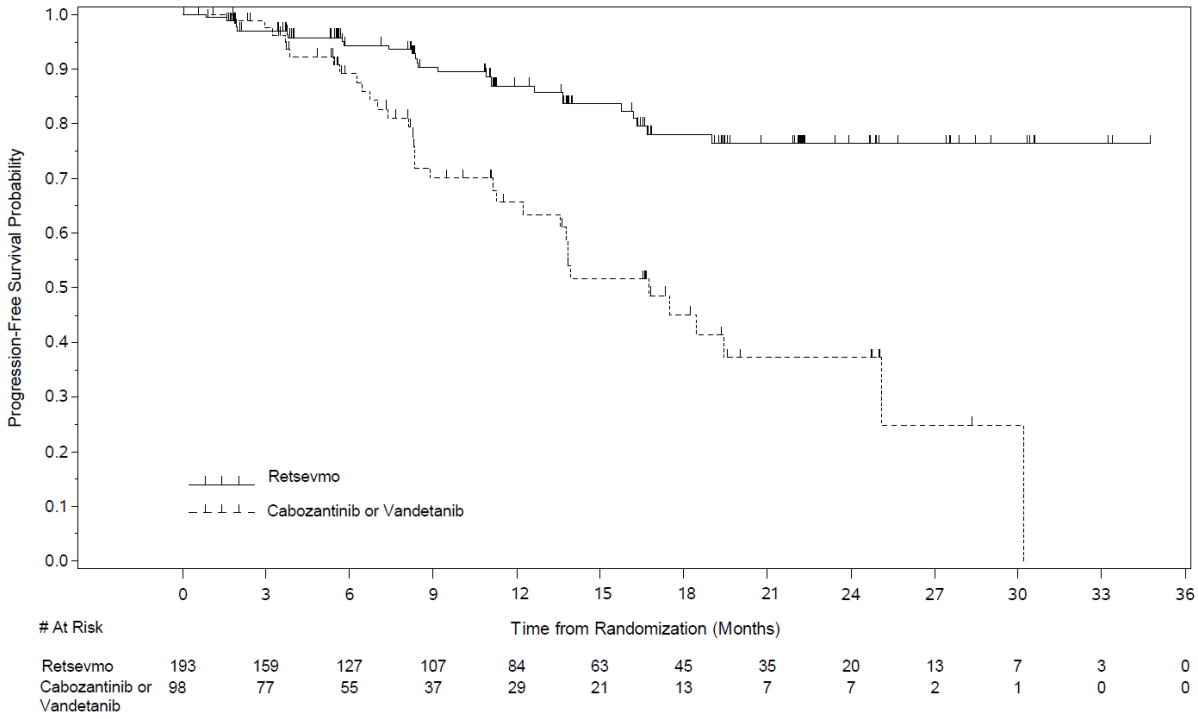
Of the 291 patients enrolled and randomised in LIBRETTO-531 to form the ITT population, 193 were randomised to the selpercatinib arm, and 98 were randomised to the control arm. Of the 98 patients randomised to the control arm, 73 were stratified to cabozantinib, and 25 were stratified to vandetanib. 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 summarised in Table 11 and Figure 2.

Table 11 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)
Rate (%) of patients with duration of response		
≥24 months (95% CI)	79.1 (66.9, 87.2)	NE (NE, NE)

NE = not estimable
*Treatment failure-free survival is defined as the time from randomisation 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.
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

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 an 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 ORR for selpercatinib was 82.4% compared to 43.9% for the control arm. OS and ORR were not powered for statistical significance.

LIBRETTO-001

Of the 324 *RET*-mutant MTC patients enrolled in LIBRETTO-001, 143 were treatment naïve to cabozantinib and vandetanib, including 116 patients who had not received any prior systemic therapy and 27 who had previously received other systemic therapy. Additionally, 152 patients were previously treated with cabozantinib and/or vandetanib and considered efficacy eligible.

The median age across the treatment naïve and treatment experienced to cabozantinib and vandetanib was 57–58 years (range 15–90), with a small proportion under 18 years of age (1.4% and 0.7%, respectively). 58.0%-63.8% patients were male, 86.7%–90.1% of patients were White, 1.3%–5.6% were Asian and 1.3%-1.4% were Black. Most patients (97.9%–98.0%) had metastatic disease at enrolment. ECOG performance status was reported as 0-1 in 92.7%–95.9% of patients, and 2 in 4.2%–7.2%. The most common mutation was M918T (60.1%–65.1%), followed by extracellular cysteine mutations (15.8%–23.8%).

Table 12 LIBRETTO-001: Objective response and duration of response for *RET*-mutant MTC

	IRC assessment	
	Treatment naïve to cabozantinib and vandetanib	**Treatment experienced to cabozantinib and/or vandetanib**
N	143	152
Objective response (CR + PR)		
% (95% CI)	82.5 (75.3, 88.4)	77.6 (70.2, 84.0)
Complete response n (%)	34 (23.8)	19 (12.5)
Partial response n (%)	84 (58.7)	99 (65.1)
Duration of response (months)*		
Median, 95% CI	NE (51.3, NE)	45.3 (33.6, NE)
Rate (%) of duration of response		
≥ 24 months (95% CI)	84.1 (75.9, 89.7)	66.4 (56.3, 74.7)

NE = not estimable.
* Treatment Naïve cabozantinib and vandetanib median duration of follow-up was 39.4 months (25th, 75th percentile: 32.3, 45.4); Treatment experienced with cabozantinib and/or vandetanib 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.

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 2980 (53%) ng/mL and AUC_{0-24h} was 51600 (58%) ng*h/mL.

Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1.

The capsule and tablet dosage forms of selpercatinib are bioequivalent.

Absorption

After an oral dose of 160 mg, RETEVMO 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%) of apparent volume of distribution (V_{ss}/F), estimated by Population PK analysis, is 203.1 L (69%) 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.

Metabolism

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

Excretion

The mean (CV%) clearance (CL/F) of selpercatinib is 5.5 L/h (45%) and the half-life is 26.5 hours following oral administration of selpercatinib in adult patients. Following oral administration of a single [^{14}C] radiolabelled 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 RETEVMO. Patients with a body weight ≤50 kg should start RETEVMO treatment with a dose of 120 mg twice daily, while patients >50 kg should start RETEVMO treatment with a dose of 160 mg twice daily.

Hepatic impairment

Selpercatinib is metabolised in the liver.

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 Dose 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 (eGFR <15 mL/min) and dialysis patients have not been studied.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Selpercatinib did not cause mutations in a bacterial mutagenicity assay and was negative in an *in vitro* micronucleus assay in human peripheral blood lymphocytes. 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.

Carcinogenicity

In a 2-year carcinogenicity study of selpercatinib in rats, vaginal tumours (vaginal carcinoma and vaginal squamous cell carcinoma) were observed in some females treated with once daily oral doses of 40 mg/kg resulting in plasma exposure (AUC) 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 in this study. No significant increase in incidences of neoplastic findings was observed in male rats treated orally once daily with 20 mg/kg for 57 weeks followed by 10 mg/kg for 31 weeks resulting in plasma exposure (AUC) levels similar to or below clinical levels observed in adult patients treated with the dose of 160 mg twice daily.

There was no evidence of carcinogenicity in male or female transgenic mice treated with once daily oral doses of up to 60 mg/kg selpercatinib for 6 months resulting in plasma exposure (AUC) approximately 4 times the levels observed in adult patients treated with the dose of 160 mg twice daily.

Juvenile animal toxicity data

Selpercatinib exposure approximately 0.3 to 0.5 times the exposure in adult humans caused mortality in rats younger than 21 days old. Exposures 3 times that in adult humans were tolerated in rats aged 21 days and older.

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

Selpercatinib caused dysplastic changes of odontoblast epithelium and dentin in the incisor teeth of adolescent and juvenile rats.

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 times the efficacious exposure in adults.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core content

Microcrystalline cellulose
Mannitol
Croscarmellose sodium
Hyprolose
Sodium stearylfumarate

Tablet film-coating

RETEVMO 40 mg film-coated tablets
Polyvinyl alcohol
Titanium dioxide
Macrogol 4000
Purified talc
Iron oxide black

RETEVMO 80 mg, and 120mg film-coated tablets
Polyvinyl alcohol
Titanium dioxide
Macrogol 4000
Purified talc
Ferric oxide
Iron oxide black

RETEVMO 160mg film-coated tablets
Polyvinyl alcohol
Titanium dioxide
Macrogol 4000
Purified talc
Ferric oxide

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

Supplied as cold formable aluminium foil (CFAF) blisters sealed with an aluminum foil lidding, in packs of 28, or 56 film-coated tablets.

Not all pack sizes may be marketed.

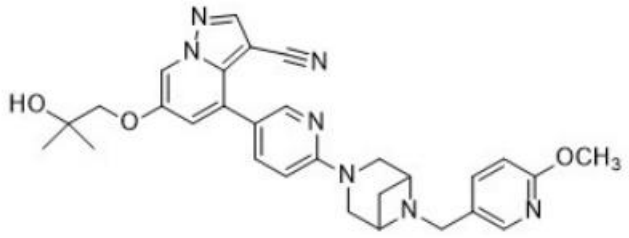
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The empirical formula for selpercatinib is $C_{29}H_{31}N_7O_3$ and it has the following structural formula.



CAS number

2152628-33-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Eli Lilly Australia Pty Ltd
Level 9, 60 Margaret Street, Sydney, NSW 2000
AUSTRALIA
Phone: 1800 454 559

9 DATE OF FIRST APPROVAL

11 August 2025

10 DATE OF REVISION

17 October 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1	Addition of indication for use in treatment of MTC
4.2	Information on paedatric population
4.4	Additional warning SCFE/SUFE
4.8	Addition of ADR erectile dysfunction and update to information about paediatric population
5.1	Clinical trials section updated with studies supporting use in MTC
4.4	Amended language under Hypothyroidism to include additional precaution for patients with insufficient response to substitution with T4.
4.8	Addition of post-marketing data *Stevens-Johnson Syndrome*

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