レットヴィモカプセル 40mg
レットヴィモカプセル 80mg
レットヴィモ錠 40mg
レットヴィモ錠 80mg
に関する資料

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レットヴィモカプセル 40mg
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1.5　起原又は発見の経緯及び開発の経緯

日本イーライリリー株式会社

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1.5　起原又は発見の経緯及び開発の経緯

セルペルカチニブは、RET のアデノシン三リン酸結合部位を競合的に阻害するよう設計された、RET 受容体型チロシンキナーゼに対して選択性の高い阻害作用を有する低分子の経口剤である。

セルペルカチニブは、既承認申請時に提出した LOXO-RET-17001 試験を主な試験成績として国内では成人及び 12 歳以上の小児において、以下の適応で承認を取得している。

- *RET* 融合遺伝子陽性の進行・再発の固形腫瘍
- *RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌

今般、*RET* 遺伝子異常を有する進行固形腫瘍又は中枢神経系原発腫瘍の小児被験者を対象とした臨床試験（J2G-OX-JZJJ）にて、*RET* 遺伝子異常を有する小児患者においても良好なベネフィット・リスクプロファイルが示されたことを踏まえ、セルペルカチニブの適応を 2 歳以上の患者に拡大するため製造販売承認事項一部変更承認申請を行うこととした。

2 歳以上の小児における *RET* 融合遺伝子陽性の進行・再発の固形腫瘍及び *RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌に対するセルペルカチニブの開発の経緯は、主に本申請資料第 2.5.1 項に記載した。表 1.5-1 に第 2 部での当該内容等の記載場所を示す。また、開発の経緯図を図 1.5-1 に示す。

表 1.5-1　第 1.5 項の内容及び第 2.5 項での記載箇所

第 1.5 項に記載する内容	第 2 部での記載場所	
起源又は発見の経緯、臨床開発の経緯、規制当局からの助言の経緯、臨床データパッケージ	2.5.1	製品開発の根拠
臨床試験の概略	2.5.2 2.5.3 2.5.4 2.5.5	生物薬剤学に関する概括評価 臨床薬理に関する概括評価 有効性の概括評価 安全性の概括評価
本剤の有効性及び安全性に基づく有用性に関する記載	2.5.6	ベネフィットとリスクに関する結論

試験項目		2019	2020	2021	2022	2023	2024	2025
臨床試験	第 1/2 相試験	[redacted]						

[redacted]

図 1.5-1　　セルペルカチニブの開発の経緯図

レットヴィモカプセル 40mg
レットヴィモカプセル 80mg
レットヴィモ錠 40mg
レットヴィモ錠 80mg

1.6　外国における使用状況等に関する資料

日本イーライリリー株式会社

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1.6　外国における使用状況等に関する資料

1.6.1　外国における申請・承認状況

セルペルカチニブは、2019 年 12 月に米国及び欧州で承認申請を行い、米国では 2020 年 5 月に、欧州では 2021 年 2 月に、*RET* 融合遺伝子陽性の非小細胞肺癌、*RET* 融合遺伝子陽性の甲状腺癌、及び *RET* 遺伝子変異陽性の甲状腺髄様癌に対して承認を取得した。また、*RET* 融合遺伝子陽性の固形がんに対しては、米国では 2022 年 9 月、欧州では 2024 年 4 月に承認された。セルペルカチニブのカプセル製剤は、2026 年 3 月時点で米国、欧州含め 50 以上の国又は地域で承認されている。セルペルカチニブの錠剤は、2026 年 3 月時点で米国、欧州含め 30 以上の国又は地域で承認されている。

セルペルカチニブの 2 歳以上 12 歳未満の小児に対する適応は、*RET* 融合遺伝子陽性の甲状腺癌、*RET* 遺伝子変異陽性の甲状腺髄様癌、及び *RET* 融合遺伝子陽性の固形がんに対して 2024 年 5 月に米国で承認されている。また、欧州で 20[redacted] 年 [redacted] 月に申請を行っている。

1.6.2　外国における添付文書

セルペルカチニブの米国の添付文書（USPI）、EUの製品概要（SmPC）及び企業中核データシート（CDS）を添付する。

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RETEVMO safely and effectively. See full prescribing information for RETEVMO.

RETEVMO® (selpercatinib) capsules, for oral use
RETEVMO® (selpercatinib) tablets, for oral use

Initial U.S. Approval: 2020

---------- RECENT MAJOR CHANGES ----------

Dosage and Administration (2.8)	11/2025
Warnings and Precautions (5.6)	11/2025

---------- INDICATIONS AND USAGE ----------

RETEVMO® is a kinase inhibitor indicated for the treatment of:

- Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *rearranged during transfection* (RET) gene fusion, as detected by an FDA-approved test (1.1)
- Adult and pediatric patients 2 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a RET mutation, as detected by an FDA-approved test, who require systemic therapy (1.2)
- Adult and pediatric patients 2 years of age and older with advanced or metastatic thyroid cancer with a RET gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate) (1.3)
- Adult and pediatric patients 2 years of age and older with locally advanced or metastatic solid tumors with a RET gene fusion, as detected by an FDA-approved test, that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options[1] (1.4)

[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

----------DOSAGE AND ADMINISTRATION----------

- Select patients for treatment with RETEVMO based on the presence of a *RET* gene fusion (NSCLC, thyroid, or other solid tumors) or specific *RET* gene mutation (MTC). (2.1, 14)
- Adult and adolescent patients 12 years of age or older:

  the recommended dosage is based on weight (2.3):
  - Less than 50 kg: 120 mg orally twice daily
  - 50 kg or greater: 160 mg orally twice daily
- Pediatric patients 2 to less than 12 years of age:

  the recommended dosage is based on body surface area (2.3):
  - 0.33 m^2 to 0.65 m^2: 40 mg orally three times daily
  - 0.66 m^2 to 1.08 m^2: 80 mg orally twice daily
  - 1.09 m^2 to 1.52 m^2: 120 mg orally twice daily
  - ≥1.53 m^2: 160 mg orally twice daily
- For patients who cannot swallow, disperse 40 mg RETEVMO tablets and administer orally or via gastrostomy or nasogastric tube (2.8)
- Only RETEVMO 40 mg tablets may be used to create the dispersion (2.2)
- Reduce RETEVMO dose in patients with severe hepatic impairment. (2.7, 8.7)

----------DOSAGE FORMS AND STRENGTHS----------

- Capsules: 40 mg, 80 mg. (3)
- Tablets: 40 mg, 80 mg, 120 mg, 160 mg. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce the dose, or permanently discontinue RETEVMO based on severity. (2.5, 5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Monitor for new or worsening pulmonary symptoms. Withhold, reduce the dose or permanently discontinue RETEVMO based on severity. (2.5, 5.2)
- Hypertension: Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure (BP) prior to initiating RETEVMO. Monitor BP after 1 week, at least monthly thereafter and as clinically indicated. Withhold, reduce the dose, or permanently discontinue RETEVMO based on severity. (2.5, 5.3)
- QT Interval Prolongation: Monitor patients who are at significant risk of developing QTc prolongation. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment. Monitor QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and reduce the dose or permanently discontinue RETEVMO based on severity. (2.5, 5.4)
- Hemorrhagic Events: Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage. (2.5, 5.5)
- Hypersensitivity: Withhold RETEVMO and initiate corticosteroids. Upon resolution, resume at a reduced dose and increase dose by 1 dose level each week until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. (2.5, 5.6)
- Tumor Lysis Syndrome: Closely monitor patients at risk and treat as clinically indicated. (5.7)
- Risk of Impaired 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. (5.8)
- Hypothyroidism: Monitor thyroid function before treatment with RETEVMO and periodically during treatment. Withhold until clinically stable or permanently discontinue based on severity. (5.9)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the possible risk to a fetus and to use effective contraception. (5.10, 8.1, 8.3)
- Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis (SCFE/SUFE) in Pediatric Patients: Monitor patients for symptoms indicative of SCFE/SUFE and treat as medically and surgically appropriate (5.11, 6.1)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥25%) include:

- Adult patients with solid tumors: edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache. (6)
- Pediatric patients with solid tumors: musculoskeletal pain, diarrhea, nausea, hemorrhage, pyrexia, abdominal pain, headache, vomiting, fatigue, cough, rash, coronavirus infection, upper respiratory tract infection, and edema. (6)

The most common Grade 3 or 4 laboratory abnormalities (≥5%) include:

- Adult patients with solid tumors: decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium. (6)
- Pediatric patients with solid tumors: decreased lymphocytes, decreased calcium, decreased hemoglobin, decreased neutrophils, increased alanine aminotransferase, decreased magnesium, and decreased potassium. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- Acid-Reducing Agents: Avoid coadministration. If coadministration cannot be avoided, take RETEVMO with food (with PPI) or modify its administration time (with H2 receptor antagonist or locally-acting antacid). (2.4, 7.1)

- Strong and Moderate CYP3A Inhibitors: Avoid coadministration. If coadministration cannot be avoided, reduce the RETEVMO dose. (2.6, 7.1)
- Strong and Moderate CYP3A Inducers: Avoid coadministration. (7.1)
- CYP2C8 and CYP3A Substrates: Avoid coadministration. If coadministration cannot be avoided, modify the substrate dosage as recommended in its product labeling. (7.2)
- Certain P-gp and BCRP Substrates: Avoid coadministration. If coadministration cannot be avoided, modify the substrate dosage as recommended in its product labeling. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: *Advise not to breastfeed.* (8.2)
- Pediatric Use: Monitor open growth plates in pediatric patients. Consider interrupting or discontinuing RETEVMO if abnormalities occur. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2025

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 *RET* Fusion-Positive Non-Small Cell Lung Cancer

RETEVMO® is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *rearranged during transfection (RET)* gene fusion, as detected by an FDA-approved test.

1.2 *RET*-Mutant Medullary Thyroid Cancer

RETEVMO is indicated for the treatment of adult and pediatric patients 2 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, as detected by an FDA-approved test, who require systemic therapy.

1.3 *RET* Fusion-Positive Thyroid Cancer

RETEVMO is indicated for the treatment of adult and pediatric patients 2 years of age and older with advanced or metastatic thyroid cancer with a *RET* gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

1.4 Other *RET* Fusion-Positive Solid Tumors

RETEVMO is indicated for the treatment of adult and pediatric patients 2 years of age and older with locally advanced or metastatic solid tumors with a *RET* gene fusion, as detected by an FDA-approved test, that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.4)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with RETEVMO based on the presence of a *RET* gene fusion (NSCLC, thyroid cancer, or other solid tumors) or specific *RET* gene mutation (MTC) in tumor specimens *[see Clinical Studies (14)]*. Information on FDA-approved test(s) for the detection of *RET* gene fusions and *RET* gene mutations is available at: http://www.fda.gov/CompanionDiagnostics. An FDA-approved companion diagnostic test for the detection of *RET* gene fusions and *RET* gene mutations in plasma is not available.

2.2 Important Administration Instructions

- RETEVMO may be taken with or without food unless coadministered with a proton pump inhibitor (PPI) [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].
- Swallow the capsule or tablet whole. Do not crush or chew the capsules or tablets.
- For patients unable to swallow capsules or tablets or who are using a feeding tube, prepare and administer RETEVMO as a dispersion; only RETEVMO 40 mg tablets may be used to create the dispersion [see Dosage and Administration (2.8)]

2.3 Recommended Dosage

The recommended dosage of RETEVMO administered as recommended *[see Dosage and Administration (2.2)]* given until disease progression or unacceptable toxicity is shown in Table 1:

Table 1: Recommended RETEVMO Dosage

Population	**RETEVMO Dosage**
Adult and adolescent patients 12 years of age or older based on body weight	
• Less than 50 kg	120 mg twice daily
• 50 kg or greater	160 mg twice daily
Pediatric patients 2 to less than 12 years of age based on body surface area	
• 0.33 to 0.65 m^2	40 mg three times daily
• 0.66 to 1.08 m^2	80 mg twice daily
• 1.09 to 1.52 m^2	120 mg twice daily
• ≥1.53 m^2	160 mg twice daily
Dosing pediatric patients with body surface area less than 0.33 m^2 is not recommended	

Missed Dose

Do not take a missed dose unless it is more than 6 hours until next scheduled dose.

Vomiting

If vomiting occurs after RETEVMO administration, do not take an additional dose and continue to the next scheduled time for the next dose.

2.4 Dosage Modifications for Concomitant Use of Acid-Reducing Agents

Avoid concomitant use of a PPI, a histamine-2 (H2) receptor antagonist, or a locally-acting antacid with RETEVMO *[see Drug Interactions (7.1)]*. If concomitant use cannot be avoided:

- Take RETEVMO with food when coadministered with a PPI.
- Take RETEVMO 2 hours before or 10 hours after administration of an H2 receptor antagonist.
- Take RETEVMO 2 hours before or 2 hours after administration of a locally-acting antacid.

2.5 Dosage Modifications for Adverse Reactions

The recommended dose reductions for adverse reactions are provided in Table 2.

Table 2: Recommended RETEVMO Dose Reductions for Adverse Reactions

Current RETEVMO Dosage	Dose Reduction		
	First	**Second**	**Third**
40 mg three times daily	40 mg twice daily	40 mg once daily	permanently discontinue
80 mg twice daily	40 mg twice daily	40 mg once daily	permanently discontinue
120 mg twice daily	80 mg twice daily	40 mg twice daily	40 mg once daily
160 mg twice daily	120 mg twice daily	80 mg twice daily	40 mg twice daily
Permanently discontinue RETEVMO in patients unable to tolerate three dose reductions.			

The recommended dosage modifications for adverse reactions are provided in Table 3.

Table 3: Recommended RETEVMO Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Hepatotoxicity *[see Warnings and Precautions (5.1)]*	Grade 3 or Grade 4	• Withhold RETEVMO and monitor AST/ALT once weekly until resolution to Grade 1 or baseline. • Resume at reduced dose by 2 dose levels and monitor AST and ALT once weekly until 4 weeks after reaching dose taken prior to the onset of Grade 3 or 4 increased AST or ALT. • Increase dose by 1 dose level after a minimum of 2 weeks without recurrence and then increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT after a minimum of 4 weeks without recurrence.
Interstitial Lung Disease/ Pneumonitis *[see Warnings and Precautions (5.2)]*	Grade 2	• Withhold RETEVMO until resolution. • Resume at a reduced dose. • Discontinue RETEVMO for recurrent ILD/pneumonitis.
	Grade 3 or Grade 4	• Discontinue RETEVMO for confirmed ILD/pneumonitis.
Hypertension *[see Warnings and*	Grade 3	• Withhold RETEVMO for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose when hypertension is controlled.

Precautions (5.3)]	Grade 4	• Discontinue RETEVMO.
QT Interval Prolongation *[see Warnings and Precautions (5.4)]*	Grade 3	• Withhold RETEVMO until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose or permanently discontinue RETEVMO.
	Grade 4	• Discontinue RETEVMO.
Hemorrhagic Events *[see Warnings and Precautions (5.5)]*	Grade 3 or Grade 4	• Withhold RETEVMO until recovery to baseline or Grade 0 or 1. • Discontinue RETEVMO for severe or life-threatening hemorrhagic events.
Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*	Grades 1-3	• Withhold RETEVMO until resolution of the event. Initiate corticosteroids. • Resume at a reduced dose by 3 dose levels while continuing corticosteroids. • Increase dose by 1 dose level each week until the dose taken prior to the onset of hypersensitivity is reached, then taper corticosteroids. • Discontinue RETEVMO for any severe skin reaction including Stevens Johnson Syndrome.
	Recurrent Grade 3 or Grade 4	• Discontinue RETEVMO.
Hypothyroidism *[see Warnings and Precautions (5.9)]*	Grade 3 or Grade 4	• Withhold RETEVMO until resolution to Grade 1 or baseline. • Discontinue RETEVMO based on severity.
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or Grade 4	• Withhold RETEVMO until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose.

2.6 Dosage Modifications for Concomitant Use of Strong and Moderate CYP3A Inhibitors

Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVMO. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the RETEVMO dose as recommended in Table 4. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume RETEVMO at the dose taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.1)]*.

Table 4: Recommended RETEVMO Dosage for Concomitant Use of Strong and Moderate CYP3A Inhibitors

Current RETEVMO Dosage	**Recommended RETEVMO Dosage**	
	Moderate CYP3A Inhibitor	**Strong CYP3A Inhibitor**
40 mg orally three times daily	40 mg orally once daily	40 mg orally once daily
80 mg orally twice daily	40 mg orally twice daily	40 mg orally twice daily
120 mg orally twice daily	80 mg orally twice daily	40 mg orally twice daily
160 mg orally twice daily	120 mg orally twice daily	80 mg orally twice daily

2.7 Dosage Modification for Severe Hepatic Impairment

Reduce the recommended dosage of RETEVMO for patients with severe hepatic impairment as recommended in Table 5 *[see Use in Specific Populations (8.7)]*.

Table 5: Recommended RETEVMO Dosage for Severe Hepatic Impairment

Current RETEVMO Dosage	Recommended RETEVMO Dosage
40 mg orally three times daily	40 mg orally twice daily
80 mg orally twice daily	40 mg orally twice daily
120 mg orally twice daily	80 mg orally twice daily
160 mg orally twice daily	80 mg orally twice daily

2.8 Alternative Administration for Patients Unable to Swallow Tablets or Capsules

For patients unable to swallow whole capsules or tablets, the 40 mg tablet may be dispersed and administered orally or via gastrostomy or nasogastric tube. Use only the 40 mg tablet to make the dispersion.

RETEVMO 40 mg tablets for Oral Administration

To prepare RETEVMO tablet as a dispersion:

1. In a glass or medicine cup, add the correct number of 40 mg RETEVMO tablets required for the prescribed dose (1, 2, 3, or 4 tablets), to approximately 1 tablespoon (15 mL) of room temperature or chilled water or 100% carrot puree.
2. Stir intermittently until tablet(s) have dispersed (approximately 7 to 10 minutes). Some settling may occur and the dispersion may appear cloudy if water is used.
3. Administer the entire dispersion immediately.
4. Add 1 tablespoon (15 mL) of water to the glass or medicine cup, swirl or stir to collect any remaining medicine and administer immediately.
5. Discard RETEVMO dispersion if not taken within 2 hours.

RETEVMO 40 mg tablets for Feeding Tubes (Gastrostomy or Nasogastric Tube) Administration

Use only polyurethane (French size 8 or larger) or vinyl chloride (French size 10 or larger) nasogastric tube or silicone (French size 14 or larger) gastrostomy tube.

1. In a glass or medicine cup, add the correct number of 40 mg RETEVMO tablet(s) required for the prescribed dose (1, 2, 3, or 4 tablets), to a minimum of 10 mL of room temperature water.
2. Stir intermittently until tablet(s) have dispersed (approximately 7 to 10 minutes). Some settling may occur and the dispersion may appear cloudy.
3. Flush the feeding tube according to manufacturer's instructions.
4. Draw the dispersion into an enteral syringe and administer the dispersion via the feeding tube immediately.
5. Add 5 mL of water to the glass or medicine cup, swirl or stir to collect any remaining medicine, and deliver this rinse via the feeding tube using the same syringe.
6. Repeat rinse as necessary to ensure full dose is delivered.
7. Flush the feeding tube according to manufacturer's instructions.
8. Discard RETEVMO dispersion if not taken within 2 hours.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 40 mg: gray opaque capsule imprinted with "Lilly", "3977" and "40 mg" in black ink.
- 80 mg: blue opaque capsule imprinted with "Lilly", "2980" and "80 mg" in black ink.

Tablets:

- 40 mg: light gray, film coated, round tablet debossed with "Ret 40" on one side and "5340" on the other side.
- 80 mg: dark red-purple, film coated, round tablet debossed with "Ret 80" on one side and "6082" on the other side.
- 120 mg: light purple, film coated, round tablet debossed with "Ret 120" on one side and "6120" on the other side.
- 160 mg: light pink, film coated, round tablet debossed with "Ret 160" on one side and "5562" on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Serious hepatic adverse reactions occurred in 3% of patients treated with RETEVMO. Increased AST occurred in 59% of patients, including Grade 3 or 4 events in 11% and increased ALT occurred in 55% of patients, including Grade 3 or 4 events in 12% *[see Adverse Reactions (6.1)]*. The median time to first onset for increased AST was 6 weeks (range: 1 day to 3.4 years) and increased ALT was 5.8 weeks (range: 1 day to 2.5 years).

Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce the dose or permanently discontinue RETEVMO based on the severity *[see Dosage and Administration (2.5)]*.

5.2 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with RETEVMO. ILD/pneumonitis occurred in 1.8% of patients who received RETEVMO, including 0.3% with Grade 3 or 4 events, and 0.3% with fatal reactions.

Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold RETEVMO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce the dose or permanently discontinue RETEVMO based on severity of confirmed ILD [*see Dosage and Administration (2.5)*].

5.3 Hypertension

Hypertension occurred in 41% of patients, including Grade 3 hypertension in 20% and Grade 4 in one (0.1%) patient *[see Adverse Reactions (6.1)]*. Overall, 6.3% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating RETEVMO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce the dose, or permanently discontinue RETEVMO based on the severity *[see Dosage and Administration (2.5)]*.

5.4 QT Interval Prolongation

RETEVMO can cause concentration-dependent QT interval prolongation *[see Clinical Pharmacology (12.2)]*. An increase in QTcF interval to >500 ms was measured in 7% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 20% of patients *[see Adverse Reactions (6.1)]*. RETEVMO has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia, and hypocalcemia prior to initiating RETEVMO and during treatment.

Monitor the QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and reduce the dose or permanently discontinue RETEVMO based on the severity *[see Dosage and Administration (2.5)]*.

5.5 Hemorrhagic Events

Serious including fatal hemorrhagic events can occur with RETEVMO. Grade ≥3 hemorrhagic events occurred in 3.1% of patients treated with RETEVMO, including 4 (0.5%) patients with fatal hemorrhagic events, including cerebral hemorrhage (n = 2), tracheostomy site hemorrhage (n = 1), and hemoptysis (n=1).

Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage *[see Dosage and Administration (2.5)]*.

5.6 Hypersensitivity

RETEVMO can cause hypersensitivity, including severe skin reactions such as Stevens Johnson Syndrome. All grade hypersensitivity occurred in 6% of patients receiving RETEVMO, including Grade 3 in 1.9%. The median time to onset was 1.9 weeks (range: 5 days to 2 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. Stevens Johnsons Syndrome has been observed in the post-marketing setting *[see Adverse Reactions (6.2)]*. Discontinue RETEVMO in patients with Stevens Johnson Syndrome.

If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity *[see Dosage and Administration (2.5)]*. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hypersensitivity.

5.7 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) occurred in 0.6% of patients with medullary thyroid carcinoma receiving RETEVMO *[see Adverse Reactions (6.1)]*. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

5.8 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.

5.9 Hypothyroidism

RETEVMO can cause hypothyroidism. Hypothyroidism occurred in 13% of patients treated with RETEVMO; all reactions were Grade 1 or 2. Hypothyroidism occurred in 13% of patients (50/373) with thyroid cancer and 13% of patients (53/423) with other solid tumors including NSCLC *[see Adverse Reactions (6.1)]*.

Monitor thyroid function before treatment with RETEVMO and periodically during treatment. Treat with thyroid hormone replacement as clinically indicated. Withhold RETEVMO until clinically stable or permanently discontinue RETEVMO based on severity *[see Dosage and Administration (2.5)]*.

5.10 Embryo-Fetal Toxicity

Based on data from animal reproduction studies and its mechanism of action, RETEVMO can cause fetal 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.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.11 Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis in Pediatric Patients

Slipped capital femoral epiphysis/slipped upper femoral epiphysis (SCFE/SUFE) occurred in 1 adolescent (2.8% of 36 patients) receiving RETEVMO in LIBRETTO-121 and 1 adolescent (0.5% of 193 patients) receiving RETEVMO in LIBRETTO-531 *[see Adverse Reactions (6.1)]*. Monitor patients for symptoms indicative of SCFE/SUFE and treat as medically and surgically appropriate *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Interstitial Lung Disease / Pneumonitis *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.4)]*
- Hemorrhagic Events *[see Warnings and Precautions (5.5)]*
- Hypersensitivity *[see Warnings and Precautions (5.6)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.7)]*
- Risk of Impaired Wound Healing *[see Warnings and Precautions (5.8)]*
- Hypothyroidism *[see Warnings and Precautions (5.9)]*
- Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis in Adolescent Patients *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety population described in the WARNINGS and PRECAUTIONS and below reflects exposure to RETEVMO as a single agent administered at 160 mg orally twice daily evaluated in 796 patients with advanced solid tumors in LIBRETTO-001 *[see Clinical Studies (14)]*.

RET Gene Fusion or Gene Mutation Positive Solid Tumors

LIBRETTO-001

Among the 796 patients who received RETEVMO, 84% were exposed for 6 months or longer and 73% were exposed for greater than one year. Among these patients, 96% received at least one dose of RETEVMO at the recommended dosage of 160 mg orally twice daily.

The median age was 59 years (range: 15 to 92 years); 0.3% were pediatric patients 12 to 16 years of age; 51% were male; and 69% were White, 23% were Asian, and 3% were Black or African American; and 5% were Hispanic/Latino. The most common tumors were NSCLC (45%), MTC (40%), and non-medullary thyroid carcinoma (7%).

Serious adverse reactions occurred in 44% of patients who received RETEVMO. The most frequent serious adverse reactions (≥2% of patients) were pneumonia, pleural effusion, abdominal pain, hemorrhage, hypersensitivity, dyspnea, and hyponatremia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions included sepsis (n = 6), respiratory failure (n = 5), hemorrhage (n = 4), pneumonia (n = 3), pneumonitis (n = 2), cardiac arrest (n=2), sudden death (n = 1), and cardiac failure (n = 1).

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received RETEVMO. Adverse reactions resulting in permanent discontinuation in ≥0.5% of patients included increased ALT (0.6%), fatigue (0.6%), sepsis (0.5%), and increased AST (0.5%).

Dosage interruptions due to an adverse reaction occurred in 64% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in ≥5% of patients included increased ALT, increased AST, diarrhea, and hypertension.

Dose reductions due to an adverse reaction occurred in 41% of patients who received RETEVMO. Adverse reactions requiring dosage reductions in ≥2% of patients included increased ALT, increased AST, QT prolongation, fatigue, diarrhea, drug hypersensitivity, and edema.

The most common adverse reactions (≥25%) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache.

The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium.

Table 6 summarizes the adverse reactions in LIBRETTO-001.

Table 6: Adverse Reactions (≥20%) in Patients Who Received RETEVMO in LIBRETTO-001

Adverse Reaction	RETEVMO (n = 796)	
	Grades 1-4# (%)	Grades 3-4 (%)
General Disorders and Administration Site Conditions		
Edema[1]	49	0.8*
Fatigue[2]	46	3.1*
Arthralgia	21	0.3*
Gastrointestinal Disorders		
Diarrhea[3]	47	5*
Dry Mouth	43	0
Abdominal pain[4]	34	2.5*
Constipation	33	0.8*
Nausea	31	1.1*
Vomiting	22	1.8*
Vascular Disorders		
Hypertension	41	20
Skin and Subcutaneous Tissue Disorders		
Rash[5]	33	0.6*
Nervous System Disorders		
Headache[6]	28	1.4*
Respiratory, Thoracic and Mediastinal Disorders		
Cough[7]	24	0
Dyspnea[8]	22	3.1
Blood and Lymphatic System Disorders		
Hemorrhage[9]	22	2.6
Investigations		
Prolonged QT interval	21	4.8*

1 Edema includes edema peripheral, face edema, periorbital edema, eye edema, eyelid edema, orbital edema, localized edema, lymphedema, scrotal edema, peripheral swelling, scrotal swelling, swelling, swelling face, eye swelling, generalized edema, genital edema.

2 Fatigue includes asthenia and malaise.

3 Diarrhea includes defecation urgency, frequent bowel movements, gastrointestinal hypermotility, anal incontinence.

4 Abdominal pain includes abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness, epigastric discomfort, gastrointestinal pain.

5 Rash includes rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash papular, rash pruritic, butterfly rash, exfoliative rash, rash follicular, rash generalized, rash vesicular.

6 Headache includes sinus headache, tension headache.

7 Cough includes productive cough, upper airway cough syndrome.

8 Dyspnea includes dyspnea exertional, dyspnea at rest.

9 Hemorrhage includes, epistaxis, hematuria, hemoptysis, contusion, rectal hemorrhage, vaginal hemorrhage, ecchymosis, hematochezia, petechiae, traumatic hematoma, anal hemorrhage, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage intracranial, hemorrhage subcutaneous, spontaneous hematoma, abdominal wall hematoma, angina bullosa hemorrhagica, conjunctival hemorrhage, disseminated intravascular coagulation, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hemorrhagic stroke, hemorrhoidal hemorrhage, hepatic hemorrhage, hepatic hematoma, intraabdominal hemorrhage, laryngeal hemorrhage, lower gastrointestinal hemorrhage, melena, mouth hemorrhage, occult blood positive, post procedural hemorrhage,

postmenopausal hemorrhage, pelvic hematoma, periorbital hematoma, periorbital hemorrhage, pharyngeal hemorrhage, pulmonary contusion, purpura, retinal hemorrhage, retroperitoneal hematoma, scleral hemorrhage, skin hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, upper gastrointestinal hemorrhage, uterine hemorrhage, vessel puncture site hematoma.

* Only includes a grade 3 adverse reaction.

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

Clinically relevant adverse reactions in ≤15% of patients who received RETEVMO include hypothyroidism (13%); pneumonia (11%), hypersensitivity (6%); interstitial lung disease/pneumonitis, chylothorax, chylous ascites or tumor lysis syndrome (all < 2%).

Table 7 summarizes the laboratory abnormalities in LIBRETTO-001.

Table 7: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-001

Laboratory Abnormality	RETEVMO[1]	
	Grades 1-4[#] (%)	Grades 3-4 (%)
Chemistry		
Increased AST	59	11
Decreased calcium	59	5.7
Increased ALT	56	12
Decreased albumin	56	2.3
Increased glucose	53	2.8
Increased creatinine	47	2.4
Decreased sodium	42	11
Increased alkaline phosphatase	40	3.4
Increased total cholesterol	35	1.7
Increased potassium	34	2.7
Decreased glucose	34	1.0
Decreased magnesium	33	0.6
Increased bilirubin	30	2.8
Hematology		
Decreased lymphocytes	52	20
Decreased platelets	37	3.2
Decreased hemoglobin	28	3.5
Decreased neutrophils	25	3.2

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 765 to 791 patients.

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

LIBRETTO-121

The safety population described below reflects exposure to RETEVMO as a single agent at 92 mg/m^2 orally twice daily evaluated in 36 patients with advanced solid tumors harboring an activating *RET* alteration in LIBRETTO-121 *[see Clinical Studies (14)]*. Among the 36 pediatric and adolescent patients who received RETEVMO, 86% were exposed for 6 months or longer and 72% were exposed for greater than one year.

The median age was 13 years (range: 2 to 20 years); 31% were pediatric patients 2 to 12 years of age; 53% were male; and 47% were White, 28% were Asian, and 8% were Black or African American; and 19% were Hispanic/Latino. The most common cancers were MTC (42%), and papillary thyroid cancer (42%).

Serious adverse reactions occurred in 42% of patients who received RETEVMO. Serious adverse reactions occurring in more than 1 patient were vomiting and fracture (2 patients each).

Dosage interruptions due to an adverse reaction occurred in 42% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in ≥5% of patients included increased ALT, increased AST, ascites, increased bilirubin, decreased neutrophils, and pyrexia.

Dose reductions due to an adverse reaction occurred in 22% of patients who received RETEVMO. Adverse reactions requiring dosage reductions in ≥2% of patients included increased ALT, decreased neutrophils, increased weight, and increased bilirubin.

The most common adverse reactions (≥25%) were musculoskeletal pain, diarrhea, nausea, hemorrhage, pyrexia, abdominal pain, headache, vomiting, fatigue, cough, rash, coronavirus infection, upper respiratory tract infection, and edema.

The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased lymphocytes, decreased calcium, decreased hemoglobin, decreased neutrophils, increased ALT, decreased magnesium, and decreased potassium.

Table 8 summarizes the adverse reactions in LIBRETTO-121.

Table 8: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-121

Adverse Reactions	RETEVMO N= 36	
	Grades 1-4# %	Grades 3-4 %
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[1]	58	0
Gastrointestinal Disorders		
Diarrhea[2]	47	2.8*
Nausea	42	2.8*
Abdominal pain[3]	36	0
Vomiting	31	8*
Constipation	22	6*
Blood and Lymphatic System Disorders		
Hemorrhage[4]	39	0
General Disorders and Administration Site Conditions		
Pyrexia	39	0
Fatigue[5]	31	0
Edema[6]	25	0
Nervous System Disorders		
Headache	33	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	31	0
Oropharyngeal pain	22	0
Skin and Subcutaneous Tissue Disorders		
Rash[7]	28	0
Infections and Infestations		
Coronavirus infection	28	0
Upper respiratory tract infection	28	2.8*
Urinary tract infection[8]	19	2.8*
Endocrine Disorders		
Hypothyroidism[9]	22	0
Investigations		
Increased weight	19	11*

1 Musculoskeletal pain includes arthralgia, back pain, bone pain, musculoskeletal chest pain, non-cardiac chest pain, neck pain, pain in extremity

2 Diarrhea includes anal incontinence

[3] Abdominal pain includes abdominal pain upper, abdominal discomfort

[4] Hemorrhage includes epistaxis, hematuria, anal hemorrhage, blood urine present, hemoptysis, menorrhagia, mouth hemorrhage

[5] Fatigue includes asthenia, malaise

[6] Edema includes face edema, edema peripheral, periorbital edema, localized edema, generalized edema, gastrointestinal edema, swelling

[7] Rash includes rash maculopapular, rash erythematous, urticaria

[8] Urinary tract infection includes cystitis

[9] Hypothyroidism includes blood thyroid stimulating hormone increased, thyroglobulin increased

* No Grade 4 events were reported.

[#] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Clinically relevant adverse reactions in <15% of patients who received RETEVMO include dizziness (14%), electrocardiogram QT prolonged (14%), hypersensitivity (11%), stomatitis (14%), proteinuria (11%), hypertension (8%), decreased appetite (8%), erectile dysfunction (6%), chylous ascites (2.8%), dry mouth (2.8%), epiphysiolysis (2.8%), and pneumonia (2.8%).

Table 9 summarizes the laboratory abnormalities in LIBRETTO-121.

Table 9: Select Laboratory Abnormalities (≥15%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-121

Laboratory Abnormality	**RETEVMO[1]**	
	Grades 1-4[#] (%)	**Grades 3-4 (%)**
Chemistry		
Decreased calcium	61	11
Increased ALT	58	8*
Decreased albumin	53	0
Increased alkaline phosphatase	50	0
Increased AST	50	2.8*
Increased bilirubin	31	2.8*
Increased cholesterol	28	0
Decreased magnesium	28	6
Increased potassium	28	2.8
Increased creatinine	19	2.8
Decreased potassium	19	6
Decreased sodium	17	0
Hematology		
Decreased neutrophils	40	8
Decreased hemoglobin	36	11*
Increased hemoglobin	33	2.8*
Decreased platelets	28	2.8*
Decreased lymphocytes	28	14

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 18 to 36 patients.

* No Grade 4 abnormalities were reported.

[#] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.

Treatment-naïve RET Fusion-Positive Non-Small Cell Lung Cancer

LIBRETTO-431

The safety population described below reflects exposure to RETEVMO as a single agent administered at 160 mg orally twice daily evaluated in 158 patients with unresectable locally advanced or metastatic *RET* fusion-positive NSCLC in LIBRETTO-431 [see Clinical Studies (14)]. Among the 158 patients who received RETEVMO, the median duration of exposure was 16.7 months (range: 5 days to 37.9 months); 87% were exposed for 6 months or longer and 70% were exposed for one year or longer.

The median age was 61 years (range: 31 to 87 years); 46% were male; and 36% were White, 58% were Asian, 1.3% were Black or African American, 1.3% were American Indian or Alaska Native, and 3.2% were missing.

Serious adverse reactions occurred in 35% of patients who received RETEVMO. The most frequent serious adverse reactions (≥2% of patients) were pleural effusion, and abnormal hepatic function. Fatal adverse reactions occurred in 4.4% of patients who received RETEVMO; fatal adverse reactions included myocardial infarction (n = 2), respiratory failure (n = 2), cardiac arrest, malnutrition, and sudden death (n = 1, each).

Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received RETEVMO. Adverse reactions resulting in permanent discontinuation in ≥1% of patients included increased ALT (1.3%), and myocardial infarction (1.3%).

Dosage interruptions due to an adverse reaction occurred in 72% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in ≥5% of patients included increased ALT, hypertension, increased AST, QT prolongation, diarrhea, and COVID-19 infection.

Dose reductions due to an adverse reaction occurred in 51% of patients who received RETEVMO. Adverse reactions requiring dose reductions in ≥5% of patients included increased ALT, increased AST, QT prolongation.

The most common adverse reactions (≥25%) in patients who received RETEVMO were hypertension, diarrhea, edema, dry mouth, rash, fatigue, abdominal pain, and musculoskeletal pain.

The most common Grade 3 or 4 laboratory abnormalities (≥5%) in patients who received RETEVMO were increased ALT, increased AST, and decreased lymphocytes.

Table 10 summarizes the adverse reactions in LIBRETTO-431.

Table 10: Adverse Reactions (≥15%) in Patients on Either Arm in LIBRETTO-431

Adverse Reaction	RETEVMO (n=158)		Chemotherapy with or without pembrolizumab (n=98)	
	Grades 1-4# (%)	Grades 3-4 (%)	Grades 1-4# (%)	Grades 3-4 (%)
Vascular disorders				
Hypertension	48	20*	7	3.1*
Gastrointestinal disorders				
Diarrhea[1]	44	1.3*	24	2.0*
Dry mouth[2]	39	0	6	0
Abdominal pain[3]	25	0.6*	19	2.0*
Constipation	22	0	40	1.0*
Stomatitis[4]	18	0	16	0
Nausea	13	0	44	1.0*
Vomiting[5]	13	0	23	1.0*
General disorders and administration site conditions				
Edema[6]	41	2.5*	28	0
Fatigue[7]	32	3.2*	50	5*

Pyrexia	13	0.6*	23	0
Skin and subcutaneous tissue disorders				
Rash[8]	33	1.9*	30	1.0*
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[9]	25	0	28	0
Investigations				
Electrocardiogram QT prolonged	20	9*	1.0	0
Infections and infestations				
COVID-19 infection	19	0.6*	18	0
Metabolism and nutrition disorders				
Decreased appetite	17	0	34	2.0*

[1] Diarrhea includes diarrhea, anal incontinence.

[2] Dry mouth includes dry mouth, mucosal dryness.

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

[4] Stomatitis includes stomatitis, mouth ulceration, mucosal inflammation.

[5] Vomiting includes vomiting, retching, regurgitation.

[6] Edema includes edema, edema peripheral, face edema, periorbital edema, swelling face, peripheral swelling, localized edema, eyelid edema, orbital edema, eye edema, scrotal edema, penile edema, orbital swelling, periorbital swelling.

[7] Fatigue includes fatigue, asthenia, malaise.

[8] Rash includes rash, rash maculopapular, skin exfoliation, rash erythematous, rash macular, dermatitis, urticaria, rash papular, dermatitis allergic, rash pustular, rash vesicular, genital rash.

[9] Musculoskeletal pain includes musculoskeletal pain, arthralgia, back pain, bone pain, musculoskeletal chest pain, non-cardiac chest pain, neck pain, pain in extremity.

* No Grade 4 abnormalities were reported.

[#] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Clinically relevant adverse reactions in <15% of patients who received RETEVMO include headache (14%); hemorrhage (13%); urinary tract infections (12%); hypothyroidism (9%); pneumonia (9%); dizziness (8%); interstitial lung disease/pneumonitis (4.4%); hypersensitivity, chylous ascites, and chylothorax (all < 2%).

Table 11 summarizes the laboratory abnormalities in LIBRETTO-431.

Table 11: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients on Either Arm in LIBRETTO-431

Laboratory Abnormality[1]	RETEVMO		Chemotherapy with or without pembrolizumab	
	Grades 1-4[#] (%)	Grades 3-4 (%)	Grades 1-4[#] (%)	Grades 3-4 (%)
Chemistry				
ALT increased	81	21	63	4.1
AST increased	77	10	46	0
Alkaline phosphatase Increased	35	1.3	22	0
Total bilirubin Increased	52	1.3	9	0
Blood creatinine Increased	23	0	21	0
Magnesium decreased	16	0.6	8	0

Laboratory Abnormality[1]	RETEVMO		Chemotherapy with or without pembrolizumab	
	Grades 1-4[#] (%)	Grades 3-4 (%)	Grades 1-4[#] (%)	Grades 3-4 (%)
Albumin decreased	25	0	5	0
Calcium decreased	53	1.9	24	1.0
Sodium decreased	31	3.2	41	2.1
Potassium decreased	17	1.3	15	1.0
Hematology				
Platelets decreased	53	3.2	39	5
Lymphocyte count decreased	53	8	64	15
Hemoglobin decreased	21	0	91	5
Neutrophil count decreased	53	2.0	58	11

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available: RETEVMO (range: 154 to 157 patients) and chemotherapy with or without pembrolizumab (range: 96 to 97 patients).

[#] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Increased Creatinine

In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed *[see Clinical Pharmacology (12.3)]*.

RET-Mutant Medullary Thyroid Cancer

LIBRETTO-531

The safety population described below reflects exposure to RETEVMO as a single agent administered at 160 mg (adults) or at 92 mg/m^2 (adolescent, not to exceed 160 mg) orally twice daily, in patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant medullary thyroid cancer in LIBRETTO-531 *[see Clinical Studies (14.2)].* Among the 193 patients who received RETEVMO, the observed median duration of exposure was 14.5 months (range: 25 days to 36 months); 80% were exposed for 6 months or longer and 59% were exposed for one year or longer.

The median age was 55 years (range: 12 to 84 years); 63% were male; and 69% were White, 28% were Asian, 2.9% were Black or African American and ethnicity was not routinely collected.

Serious adverse reactions occurred in 22% of patients who received RETEVMO. The most frequent serious adverse reactions were pneumonia and pyrexia (n = 3, each) and hypertension and urinary tract infection (n = 2, each). Fatal adverse reactions occurred in 2.1% of patients; fatal adverse reactions included COVID-19, diabetic ketoacidosis, multiple organ dysfunction syndrome, and sudden death (n=1 each).

Permanent discontinuation due to an adverse reaction occurred in 4.7% of patients who received RETEVMO. Adverse reactions resulting in permanent discontinuation were edema, multiple organ dysfunction syndrome, sudden death, AST increased, diabetic ketoacidosis, chronic kidney disease, retinopathy, COVID-19, and somatic symptom disorder (n = 1, each).

Dosage interruptions due to an adverse reaction occurred in 49% of patients who received RETEVMO. Adverse reactions requiring dosage omission in ≥5% of patients included ALT increased (9%) and hypertension (7%).

Dose reductions due to an adverse reaction occurred in 39% of patients who received RETEVMO. One adverse reaction, increased ALT (7%), required a dose reduction in ≥5% of patients.

The most common adverse reactions (≥25%) in patients who received RETEVMO were hypertension, edema, dry mouth, fatigue, and diarrhea.

The most common Grade 3 or 4 laboratory abnormalities (≥5%) in patients who received RETEVMO were decreased lymphocytes, increased ALT, decreased neutrophils, increased ALP, increased blood creatinine, decreased calcium, and increased AST.

Table 12 summarizes the adverse reactions in LIBRETTO-531.

Table 12: Adverse Reactions (≥10%) in Patients Who Received RETEVMO in LIBRETTO-531

Adverse Reaction	RETEVMO N = 193		Cabozantinib or Vandetanib N = 97	
	Grades 1-4# (%)	Grades 3-4 (%)	Grades 1-4# (%)	Grades 3-4 (%)
Vascular disorders				
Hypertension[1]	43	19*	41	18*
General disorders and administration-site conditions				
Edema[2]	33	0	5	0
Fatigue[3]	28	4.1*	47	9*
Pyrexia	12	1.0*	2.1	0
Gastrointestinal disorders				
Dry mouth[4]	32	0.5*	10	1.0*
Diarrhea[5]	26	3.1*	61	8*
Abdominal pain[6]	18	0.5*	21	2.1*
Constipation	16	0	12	0
Stomatitis[7]	14	0.5*	42	13*
Pyrexia	12	1.0*	2.1	0
Nausea	10	1.0*	32	5*
Nervous system disorders				
Headache[8]	23	0.5*	21	0
Skin and subcutaneous tissue disorders				
Rash[9]	19	1.6*	27	4.1*
Reproductive system and breast disorders				
Erectile dysfunction	16	0	0	0
Investigations				
Electrocardiogram QT prolonged[10]	14	4.7*	13	2.1*
Metabolism and nutrition disorders				
Decreased appetite	12	0.5*	28	5*
Endocrine disorders				
Hypothyroidism[11]	11	0	21	0

1 Hypertension includes hypertension, blood pressure increased.

2 Edema includes edema peripheral, face edema, periorbital edema, swelling face, peripheral swelling, localized edema, eyelid edema, generalized edema, eye swelling, lymphoedema, orbital edema, eye edema, edema, edema genital, swelling, scrotal edema, scrotal swelling, angioedema, skin edema, testicular swelling, vulvovaginal swelling.

3 Fatigue includes fatigue, asthenia, malaise.

4 Dry mouth includes dry mouth, mucosal dryness.

5 Diarrhea includes diarrhea, anal incontinence, defecation urgency, frequent bowel movements, gastrointestinal hypermotility.

6 Abdominal pain included abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, gastrointestinal pain.

7 Stomatitis includes stomatitis, mouth ulceration, mucosal inflammation.

8 Headache includes headache, sinus headache, tension headache.

[9] Rash includes rash, rash maculopapular, skin exfoliation, rash erythematous, rash macular, dermatitis, urticaria, rash pruritic, exfoliative rash, rash papular, dermatitis allergic, rash follicular, rash generalized, rash pustular, butterfly rash, rash morbilliform, rash vesicular.

[10] Electrocardiogram QT prolongation includes electrocardiogram QT prolonged, electrocardiogram QT interval abnormal.

[11] Hypothyroidism includes hypothyroidism, blood thyroid stimulating hormone increased.

* Only includes a Grade 3 adverse reaction

[#] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

Clinically relevant adverse reactions in ≤10% of patients who received RETEVMO include dizziness (8%); urinary tract infections (8%); vomiting (8%); pneumonia, interstitial lung disease/pneumonitis, chylous ascites, and hypersensitivity (all < 2%).

Table 13 summarizes the laboratory abnormalities in LIBRETTO-531.

Table 13: Select Laboratory Abnormalities (≥5%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-531

Laboratory Abnormality	RETEVMO[1]		Cabozantinib or Vandetanib[1]	
	Grades 1-4[#] %	Grades 3-4 %	Grades 1-4[#] %	Grades 3-4 %
Chemistry				
Calcium decreased	55	5	62	11
ALT increased	53	16	72	7*
AST increased	47	5	68	3.2*
Alkaline phosphatase increased	37	6	28	5
Total bilirubin increased	32	1.1	30	3.2*
Blood creatinine increased	27	6	16	8
Sodium decreased	20	3.2*	16	0
Albumin decreased	11	1.1	7	0
Magnesium decreased	9	3.3	26	9
Potassium decreased	8	0	22	4.4*
Hematology				
Lymphocyte count decreased	41	18	36	13
Neutrophil count decreased	33	14	42	19
Platelets decreased	28	1.1	34	1.1*
Hemoglobin decreased	18	2.1*	23	2.1*

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available: RETEVMO (range: 183 to 191 patients) and chemotherapy with or without cabozantinib or vandetanib (range: 91 to 94 patients).

* Only includes a Grade 3 laboratory abnormality

[#] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

Increased Creatinine

In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed *[see Clinical Pharmacology (12.3)]*.

6.2 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of RETEVMO. Because such reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on RETEVMO

Acid-Reducing Agents

Concomitant use of RETEVMO with acid-reducing agents decreases selpercatinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce RETEVMO anti-tumor activity.

Avoid concomitant use of PPIs, H2 receptor antagonists, and locally-acting antacids with RETEVMO. If coadministration cannot be avoided, take RETEVMO with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid) *[see Dosage and Administration (2.4)]*.

Strong and Moderate CYP3A Inhibitors

Concomitant use of RETEVMO with a strong or moderate CYP3A inhibitor increases selpercatinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of RETEVMO adverse reactions, including QTc interval prolongation.

Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVMO. If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the RETEVMO dosage and monitor the QT interval with ECGs more frequently *[see Dosage and Administration (2.6), Warning and Precautions (5.4)]*.

Strong and Moderate CYP3A Inducers

Concomitant use of RETEVMO with a strong or moderate CYP3A inducer decreases selpercatinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce RETEVMO anti-tumor activity.

Avoid coadministration of strong or moderate CYP3A inducers with RETEVMO.

7.2 Effects of RETEVMO on Other Drugs

CYP2C8 and CYP3A Substrates

RETEVMO is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of RETEVMO with CYP2C8 and CYP3A substrates increases their plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVMO with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Certain P-gp and BCRP Substrates

RETEVMO is a P-gp and BCRP inhibitor. Concomitant use of RETEVMO with P-gp or BCRP substrates increases their plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVMO with P-gp or BCRP substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for P-gp and BCRP substrates provided in their approved product labeling.

7.3 Drugs that Prolong QT Interval

RETEVMO is associated with QTc interval prolongation *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.2)]*. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies, and its mechanism of action *[see Clinical Pharmacology (12.1)]*, RETEVMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVMO use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryolethality and malformations at maternal exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥100 mg/kg [approximately 3.6 times the human exposure based on the area under the curve (AUC) at the clinical dose of 160 mg twice daily] resulted in 100% post-implantation loss. At the dose of 50 mg/kg [approximately equal to the human exposure (AUC) at the clinical dose of 160 mg twice daily], 6 of 8 females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

8.2 Lactation

Risk Summary

There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with RETEVMO and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Based on animal data, RETEVMO can cause embryolethality and malformations at doses resulting in exposures less than or equal to the human exposure at the clinical dose of 160 mg twice daily *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating RETEVMO *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose.

Infertility

RETEVMO may impair fertility in females and males of reproductive potential *[see Use in Specific Populations (8.4), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of RETEVMO have been established in pediatric patients aged 2 years and older for the treatment of:

- advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation who require systemic therapy
- advanced or metastatic thyroid cancer with a *RET* gene fusion who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate)
- locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

Use of RETEVMO for these indications is supported by evidence from adequate and well-controlled studies in adult and pediatric patients with additional pharmacokinetic and safety data in pediatric patients aged 2 years and older *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2, 14.3, 14.4)]*. The predicted exposures of selpercatinib in pediatric patients at the recommended dosages were within the range of values observed in patients ≥ 12 years and ≥ 50 kg in body weight receiving the approved recommended dosage of 160 mg twice daily *[see Clinical Pharmacology (12.3)]*.

The safety and effectiveness of RETEVMO have not been established in these indications in patients aged less than 2 years.

The safety and effectiveness of RETEVMO have not been established in pediatric patients for other indications *[see Indications and Usage (1)]*.

Juvenile Animal Toxicity Data

In a juvenile rat toxicity study, animals were dosed daily with selpercatinib from post-natal day 21 to day 70 (approximately equivalent to a human child to late adolescent). Selpercatinib increased physeal thickness of multiple bones, extending into the metaphysis and associated with decreased trabecular bone, which was not reversible at doses approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily. Growth plate changes were associated with impairment of bone modeling, resulting in decreased femur length and with reduction in bone mineral density. Selpercatinib also induced reversible hypocellularity of bone marrow in males at ≥30 mg/kg (approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily), and reversible alterations of dentin composition at ≥50 mg/kg (approximately 3 times the adult human exposure at the clinical dose of 160 mg twice daily). Irreversible, dose-dependent degeneration of testicular germinal epithelium, with vacuolation of Sertoli cells and corresponding depletion of spermatozoa in the epididymides, was also observed at ≥ 30 mg/kg (approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily) and affected male reproductive performance at 50 mg/kg (approximately 3 times the adult human exposure at the clinical dose of 160 mg twice daily). Females exhibited delay in attainment of vaginal patency, a marker of sexual maturity, at 125 mg/kg (approximately 4 times the adult human exposure at the clinical dose of 160 mg twice daily); this effect was associated with lower mean body weight. Similar effects in irregular thickening of growth plates in adult rats and minipigs, and tooth dysplasia and malocclusion, resulting in tooth loss in adult rats were observed in repeat dose studies of up to 13-week duration with selpercatinib.

Monitor growth plates in pediatric patients with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment.

8.5 Geriatric Use

Of 796 patients who received RETEVMO, 34% (268 patients) were ≥65 years of age and 9% (74 patients) were ≥75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were ≥65 years of age and younger patients.

8.6 Renal Impairment

No dosage modification is recommended for patients with mild to severe renal impairment [estimated Glomerular Filtration Rate (eGFR) ≥15 to 89 mL/min, estimated by Modification of Diet in Renal Disease (MDRD) equation].

The recommended dosage has not been established for patients with end-stage renal disease (ESRD) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

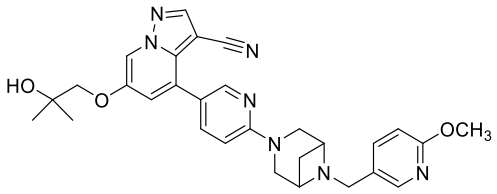
Reduce the dose when administering RETEVMO to patients with severe [total bilirubin > 3 to 10 × upper limit of normal (ULN) and any AST] hepatic impairment *[see Dosage and Administration (2.7)]*.

No dosage modification is recommended for patients with mild (total bilirubin ≤ ULN with AST > ULN or total bilirubin > 1 to 1.5 × ULN with any AST) or moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment.

Monitor for RETEVMO-related adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

RETEVMO contains selpercatinib, a kinase inhibitor. The molecular formula for selpercatinib is $C_{29}H_{31}N_7O_3$ and the molecular weight is 525.61 g/mol. The chemical name is 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. Selpercatinib has the following chemical structure:



Selpercatinib is a white to light yellow powder that is slightly hygroscopic. The aqueous solubility of selpercatinib is pH dependent, from sparingly soluble at low pH to practically insoluble at neutral pH.

RETEVMO capsules contain either 40 mg or 80 mg of selpercatinib in hard gelatin capsules for oral use. Each capsule contains inactive ingredients of colloidal silicon dioxide and microcrystalline cellulose. The 40 mg capsule shell is composed of gelatin, titanium dioxide, ferric oxide black and black ink. The 80 mg capsule shell is composed of gelatin, titanium dioxide, FD&C blue #1 and black ink. The black ink is composed of shellac, potassium hydroxide and ferric oxide black.

RETEVMO tablets contain 40 mg, 80 mg, 120 mg, or 160 mg of selpercatinib as film coated, debossed tablets for oral use. Each tablet contains inactive ingredients of croscarmellose sodium, hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet film coating material contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc. Additionally, the film coating of the 40 mg, 80 mg, and 120 mg tablets contains ferrosoferric oxide and the film coating of the 80 mg, 120 mg, and 160 mg tablets contain ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Selpercatinib is a kinase inhibitor. Selpercatinib inhibited wild-type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3 with IC_{50} 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 cellular assays, selpercatinib inhibited RET at approximately 60-fold lower concentrations than FGFR1 and 2 and approximately 8-fold lower concentration than VEGFR3.

Certain point mutations in *RET* or chromosomal rearrangements involving in-frame fusions of *RET* with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers by promoting cell proliferation of tumor cell lines. In in vitro and in vivo tumor models, selpercatinib demonstrated anti-tumor activity in cells harboring constitutive activation of RET proteins resulting from gene fusions and mutations, including CCDC6-RET, KIF5B-RET, RET V804M, and RET M918T. In addition, selpercatinib showed anti-tumor activity in mice intracranially implanted with a patient-derived *RET* fusion positive tumor.

12.2 Pharmacodynamics

Exposure-Response Relationship

Selpercatinib exposure-response relationships and the time course of pharmacodynamic response have not been fully characterized.

Cardiac Electrophysiology

The effect of RETEVMO on the QTc interval was evaluated in a thorough QT study in healthy subjects. The largest mean increase in QTc is predicted to be 10.6 msec (upper 90% confidence interval: 12.1 msec) at the mean steady-state maximum concentration (C_{max}) observed in patients after administration of 160 mg twice daily. The increase in QTc was concentration-dependent.

12.3 Pharmacokinetics

The pharmacokinetics of selpercatinib capsules were evaluated in patients with locally advanced or metastatic solid tumors administered 160 mg twice daily unless otherwise specified. The capsule and tablet dosage forms of selpercatinib are bioequivalent. Steady state selpercatinib AUC and C_{max} increased in a slightly greater than dose proportional manner over the dose range of 20 mg once daily to 240 mg twice daily [0.06 to 1.5 times the maximum recommended total daily dosage].

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 AUC_{0-24h} was 51,600 (58%) ng*h/mL.

Absorption

The median t_{max} of selpercatinib is 2 hours. The mean absolute bioavailability of RETEVMO capsules is 73% (60% to 82%) in healthy subjects.

Effect of Food

For both the capsule and tablet dosage forms no clinically significant differences in selpercatinib AUC or C_{max} were observed following administration of a high-fat meal (approximately 900 calories, 58 grams carbohydrate, 56 grams fat and 43 grams protein) in healthy subjects.

Distribution

The apparent volume of distribution (V_{ss}/F) of selpercatinib is 203 L.

Protein binding of selpercatinib is 96% in vitro and is independent of concentration. The blood-to-plasma concentration ratio is 0.7.

Elimination

The apparent clearance (CL/F) of selpercatinib is 6 L/h in patients and the half-life is 32 hours following oral administration of RETEVMO in healthy subjects.

Metabolism

Selpercatinib is metabolized predominantly by CYP3A4. Following oral administration of a single radiolabeled 160 mg dose of selpercatinib to healthy subjects, unchanged selpercatinib constituted 86% of the radioactive drug components in plasma.

Excretion

Following oral administration of a single radiolabeled 160 mg dose of selpercatinib to healthy subjects, 69% of the administered dose was recovered in feces (14% unchanged) and 24% in urine (12% unchanged).

Specific Populations

The apparent volume of distribution and clearance of selpercatinib increase with increasing body weight (9.6 kg to 179 kg).

No clinically significant differences in the pharmacokinetics of selpercatinib were observed based on age (2 years to 92 years), sex, or mild, moderate, or severe renal impairment (eGFR ≥15 to 89 mL/min). The effect of ESRD on selpercatinib pharmacokinetics has not been studied.

Pediatric patients

The exposures of selpercatinib in pediatric patients are comparable to those in adult patients administered at the recommended dosages.

Patients with Hepatic Impairment

The selpercatinib $AUC_{0\text{-}INF}$ increased 1.1-fold in subjects with mild (total bilirubin ≤ ULN with AST > ULN or total bilirubin > 1 to 1.5 × ULN with any AST), 1.3-fold in subjects with moderate (total bilirubin > 1.5 to 3 × ULN and any AST), and 1.8-fold in subjects with severe (total bilirubin > 3 to 10 × ULN and any AST) hepatic impairment, compared to subjects with normal hepatic function.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Proton-Pump Inhibitors (PPI): Coadministration with multiple daily doses of omeprazole (PPI) decreased selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when RETEVMO was administered fasting. Coadministration 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 (Table 14).

Table 14: Change in Selpercatinib Exposure After Coadministration with PPI

	Selpercatinib $AUC_{0\text{-}INF}$	**Selpercatinib C_{max}**
RETEVMO fasting	Reference	Reference
RETEVMO fasting + PPI	↓ 69%	↓ 88%
RETEVMO with a high-fat meal[1] + PPI	↑ 2%	↓ 49%
RETEVMO with a low-fat meal[2] + PPI	No change	↓ 22%

[1] High-fat meal: approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively; approximately 800 to 1,000 calories total.

[2] Low-fat meal: approximately 390 calories and 10 g of fat.

H2 Receptor Antagonists: No clinically significant differences in selpercatinib pharmacokinetics were observed when coadministered with multiple daily doses of ranitidine (H2 receptor antagonist) given 10 hours prior to and 2 hours after the RETEVMO dose (administered fasting).

Strong CYP3A Inhibitors: Coadministration of multiple doses of itraconazole (strong CYP3A inhibitor) increased the selpercatinib $AUC_{0\text{-}INF}$ 2.3-fold and C_{max} 1.3-fold.

Moderate CYP3A Inhibitors: Coadministration of multiple doses of diltiazem, fluconazole, or verapamil (moderate CYP3A inhibitors) is predicted to increase the selpercatinib AUC 1.6 to 2-fold and C_{max} 1.5 to 1.8-fold.

Strong CYP3A Inducers: Coadministration of multiple doses of rifampin (strong CYP3A inducer) decreased the selpercatinib $AUC_{0\text{-}INF}$ by 87% and C_{max} by 70%.

Moderate CYP3A Inducers: Coadministration of multiple doses of bosentan or efavirenz (moderate CYP3A inducers) is predicted to decrease the selpercatinib AUC by 40-70% and C_{max} by 34-57%.

Weak CYP3A Inducers: Coadministration of multiple doses of modafinil (weak CYP3A inducer) is predicted to decrease the selpercatinib AUC by 33% and C_{max} by 26%.

CYP2C8 Substrates: Coadministration of RETEVMO with repaglinide (sensitive CYP2C8 substrate) increased the repaglinide $AUC_{0\text{-}INF}$ 2.9-fold and C_{max} 1.9-fold.

CYP3A Substrates: Coadministration of RETEVMO with midazolam (sensitive CYP3A substrate) increased the midazolam $AUC_{0\text{-}INF}$ 1.5-fold and C_{max} 1.4-fold.

P-glycoprotein (P-gp) Substrates: Coadministration of RETEVMO with dabigatran (P-gp substrate) increased the dabigatran $AUC_{0\text{-}INF}$ 1.4-fold and C_{max} 1.4-fold.

BCRP Substrates: Coadministration of RETEVMO with rosuvastatin (BCRP substrate) increased the rosuvastatin $AUC_{0\text{-}INF}$ by 1.9-fold and C_{max} by 1.7-fold.

P-gp Inhibitors: No clinically significant differences in selpercatinib pharmacokinetics were observed when coadministered with a single dose of rifampin (P-gp inhibitor).

MATE1 Substrates: No clinically significant differences in glucose levels were observed when metformin (MATE1 substrate) was coadministered with selpercatinib.

In Vitro Studies

CYP Enzymes: Selpercatinib does not inhibit or induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations.

Transporter Systems: Selpercatinib inhibits MATE1. Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1 *[see Adverse Reactions (6.1)]*.

Selpercatinib does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, and MATE2-K at clinically relevant concentrations.

Selpercatinib is a substrate for P-gp and BCRP, but not for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Selpercatinib was not carcinogenic in a 2-year study in rats when administered by daily oral gavage at doses up to 20 mg/kg in males or 40 mg/kg in females (approximately equal to the human exposure by AUC at the 160 mg twice daily clinical dose). Selpercatinib was not carcinogenic in a 6-month study in rasH2 transgenic mice when administered by daily oral gavage at doses of up to 60 mg/kg.

Selpercatinib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assays, with or without metabolic activation, or clastogenic in the in vitro micronucleus assay in human peripheral lymphocytes, with or without metabolic activation. Selpercatinib was positive in the in vivo micronucleus assay in rats at concentrations >7 times the C_{max} at the human dose of 160 mg twice daily.

In general toxicology studies, male rats and minipigs exhibited testicular degeneration which was associated with luminal cell debris and/or reduced luminal sperm in the epididymis at selpercatinib exposures approximately 0.4 (rat) and 0.1 (minipig) times the clinical exposure by AUC at the 160 mg twice daily clinical dose. In a dedicated fertility study in male rats, administration of selpercatinib at doses up to 30 mg/kg/day (approximately twice the clinical exposure by AUC at the 160 twice daily clinical dose) for 28 days prior to cohabitation with untreated females did not affect mating or have clear effects on fertility. Males did, however, display a dose-dependent increase in testicular germ cell depletion and spermatid retention at doses ≥3 mg/kg (~0.2 times the clinical exposure by AUC at the 160 twice daily clinical dose) accompanied by altered sperm morphology at 30 mg/kg.

In a dedicated fertility study in female rats treated with selpercatinib for 15 days before mating to Gestational Day 7, there were decreases in the number of estrous cycles at a dose of 75 mg/kg (approximately equal to the human exposure by AUC at the 160 mg twice daily clinical dose). While selpercatinib did not have clear effects on mating performance or ability to become pregnant at any dose level, half of females at the 75 mg/kg dose level had 100% nonviable embryos. At the same dose level in females with some viable embryos there were increases in post-implantation loss. In a 3-month general toxicology study in minipigs, there were findings of decreased or absent corpora lutea at a selpercatinib dose of 15 mg/kg (approximately 0.3 times to the human exposure by AUC at the 160 mg twice daily clinical dose). Corpora luteal cysts were present in the minipig at selpercatinib doses ≥2 mg/kg (approximately 0.07 times the human exposure by AUC at the 160 mg twice daily clinical dose).

14 CLINICAL STUDIES

14.1 *RET* Fusion-Positive Non-Small Cell Lung Cancer

LIBRETTO-001

The efficacy of RETEVMO was evaluated in patients with advanced *RET* fusion-positive NSCLC enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). The study enrolled patients with advanced or metastatic *RET* fusion-positive NSCLC who had progressed on platinum-based chemotherapy and patients with locally advanced (stage III who were not candidates for surgical resection or definitive chemoradiation) or metastatic NSCLC without prior systemic therapy in separate cohorts. Identification of a *RET* gene alteration was prospectively determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH) or other local testing methods. Adult patients received RETEVMO 160 mg orally twice daily until unacceptable toxicity or disease progression; patients enrolled in the dose escalation phase were permitted to adjust their dose to 160 mg twice daily. The major efficacy outcome measures were confirmed overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

RET Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy

Efficacy was evaluated in 247 patients with *RET* fusion-positive NSCLC previously treated with platinum chemotherapy enrolled into a cohort of LIBRETTO-001.

The median age was 61 years (range: 23 to 81); 57% were female; 44% were White, 48% were Asian, 4.9% were Black or African American; and 2.8% were Hispanic/Latino. ECOG performance status was 0-1 (97%) or 2 (3%) and 97% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range 1–15); 58% had prior anti-PD1/PD-L1 therapy. *RET* fusions were detected in 94% of patients using NGS (84.6% tumor samples; 9.3% blood or plasma samples), 4.0% using FISH, 1.6% using PCR and 0.4% by other local testing methods.

Efficacy results for previously treated *RET* fusion-positive NSCLC are summarized in Table 15.

Table 15: Efficacy Results in LIBRETTO-001 (*RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy)

	RETEVMO (n = 247)
Overall Response Rate[1] (95% CI)	61% (55%, 67%)
Complete response	7.3%
Partial response	54%
Duration of Response	
Median in months (95% CI)	28.6 (20, NE)
% with ≥ 12 months[2]	63%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

For the 144 patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, an exploratory subgroup analysis of ORR was 63% (95% CI: 54%, 70%) and the median DOR was 28.6 months (95% CI: 14.8, NE).

Among the 247 patients with previously treated *RET* fusion-positive NSCLC, 16 had measurable CNS metastases at baseline as assessed by BIRC. One patient received radiation therapy (RT) to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 14 of these 16 patients; 39% of responders had an intracranial DOR of ≥ 12 months.

Treatment-naïve *RET* Fusion-Positive NSCLC

Efficacy was evaluated in 69 patients with treatment-naïve *RET* fusion-positive NSCLC enrolled into a cohort of LIBRETTO-001.

The median age was 63 years (range 23 to 92); 62% were female; 70% were White, 19% were Asian, and 6% were Black or African American. ECOG performance status was 0-1 (94%) or 2 (6%) and 99% of patients had metastatic disease. *RET* fusions were detected in 91% of patients using NGS (60.9% tumor samples; 30.4% in blood), 7.2% using FISH and 1.4% using PCR.

Efficacy results for treatment naïve *RET* fusion-positive NSCLC are summarized in Table 16.

Table 16: Efficacy Results in LIBRETTO-001 (Treatment-Naïve *RET* Fusion-Positive NSCLC)

	RETEVMO (n =69)
Overall Response Rate[1] (95% CI)	84% (73%, 92%)
Complete response	5.8%
Partial response	78%
Duration of Response	
Median in months (95% CI)	20.2 (13, NE)
% with ≥ 12 months[2]	50%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

Among the 69 patients with treatment-naïve *RET* fusion-positive NSCLC, 5 had measurable CNS metastases at baseline as assessed by BIRC. Two patients received RT to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 4 of these 5 patients; 38% of responders had an intracranial DOR of ≥ 12 months.

LIBRETTO-431

The efficacy of RETEVMO was evaluated in patients with unresectable, locally advanced or metastatic, *RET* fusion-positive NSCLC enrolled in a multicenter, open-label, active-controlled, randomized trial (LIBRETTO-431, NCT04194944). The trial evaluated RETEVMO compared to platinum-based and pemetrexed chemotherapy with or without pembrolizumab in patients with *RET* fusion-positive, unresectable locally advanced or metastatic NSCLC with no previous systemic therapy for metastatic disease.

Patients (N=261) were randomized to receive either RETEVMO (160 mg orally twice daily) in continuous 21-day cycles or pemetrexed intravenously (IV) (500 mg per square meter of body-surface area) along with the investigator's choice of platinum therapy (carboplatin IV [AUC 5, maximum dose 750 mg] or cisplatin IV [75 mg per square meter]) with or without pembrolizumab IV (200 mg) every 21 days. Treatment continued until disease progression or unacceptable toxicity. Crossover from the control arm to RETEVMO was permitted following disease progression. Patients were stratified according to geographic region (East Asia vs. elsewhere), brain metastases at baseline (presence vs. absence or unknown), and the investigator's intent (before randomization) to treat the patient with or without pembrolizumab. Tumor assessments were performed every 6 weeks for two assessments, then every 9 weeks for four assessments, and then every 12 weeks thereafter.

The major efficacy outcome measure was progression-free survival (PFS) in patients intended to be treated with chemotherapy in combination with pembrolizumab and in the overall study population as determined by a blinded independent review committee (BIRC) according to RECIST v1.1. Other efficacy outcome measures included overall survival (OS) and overall response rate (ORR).

A total of 212 patients were enrolled in LIBRETTO-431 with an intent to treat with pembrolizumab if randomized to the control arm (129 into RETEVMO arm and 83 into chemotherapy with pembrolizumab arm). The median age was 61.5

years (range: 31 to 84 years); 47% were male; 41% White, 55% Asian, and 0.9% Black or African American, 1.4% American Indian or Alaska Native, 1.9% were race not reported; ethnicity was not reported in 96% of patients. ECOG performance status was 0-1 (97%) or 2 (3%), 68% were never smokers, 93% of patients had metastatic disease, and 14% had measurable intracranial metastases at baseline, as determined by a neuroradiologic BIRC. RET fusions were detected in 60% of patients using NGS and 40% using PCR (89% tumor samples; 11% in blood).

Efficacy results from the pre-planned interim efficacy analysis are summarized in Table 17.

Table 17: Efficacy Results in LIBRETTO-431: RETEVMO versus Chemotherapy with Pembrolizumab

	RETEVMO (n = 129)	**Chemotherapy with pembrolizumab (n = 83)**
Progression-Free Survival		
Number (%) of patients with an event	49 (38%)	49 (59%)
Medians in months (95% CI)	24.8 (16.9, NE)	11.2 (8.8, 16.8)
Hazard ratio[1] (95% CI)	0.46 (0.31, 0.70)	
p-value[2]	0.0002	
Overall Response Rate (95% CI)	84% (76, 90)	65% (54, 75)
Complete response	7%	6%
Partial response	77%	59%
Duration of Response		
Median in months (95% CI) % with ≥ 12 months[3]	24.2 (17.9, NE) 60%	11.5 (9.7, 23.3) 30%

[1] Based on the stratified Cox proportional hazard model, stratified by geographic location (East Asia versus elsewhere), brain metastases at baseline according to investigator (presence versus absence or unknown).

[2] Based on stratified log-rank test, stratified by geographic location (East Asia versus elsewhere), brain metastases at baseline according to investigator (presence versus absence or unknown).

[3] Based on observed duration of response.

NE = not estimable

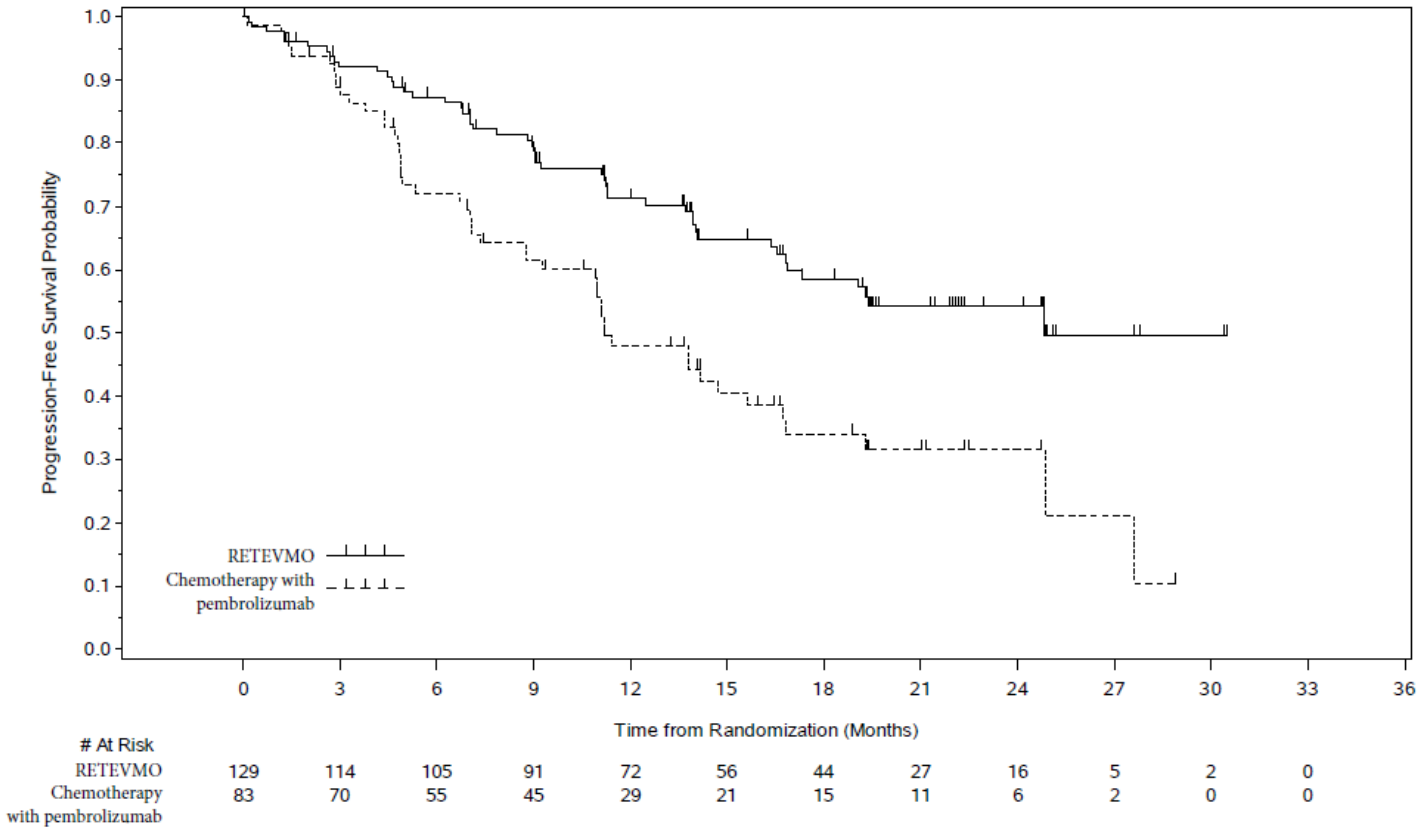


Figure 1: Kaplan-Meier Curves of Progression-Free Survival in LIBRETTO-431: RETEVMO versus Chemotherapy with Pembrolizumab

Among the 212 randomized patients, 29 had measurable CNS metastases at baseline as assessed by BIRC. Responses in intracranial lesions were observed in 14 of 17 patients treated with RETEVMO and 7 of 12 patients treated with chemotherapy with pembrolizumab.

Overall survival was immature at the time of the PFS interim analysis. At the time of an updated descriptive analysis of OS (43% of prespecified OS events needed for the final analysis), a total of 49 (31%) and 26 (25%) patients died in the RETEVMO and the control arm, respectively. The OS HR was 1.26 (95% CI: 0.78, 2.04). Overall survival may be affected by the imbalance in post-progression therapies. Of 68 control arm patients who had disease progression, 50 patients (74%) received RETEVMO at progression. Of 71 RETEVMO arm patients who had disease progression, 16 (23%) received chemotherapy and/or immune checkpoint inhibitor therapy, and 44 (62%) continued receiving RETEVMO.

14.2 *RET*-Mutant Medullary Thyroid Cancer

LIBRETTO-001

The efficacy of RETEVMO was evaluated in patients with *RET*-mutant MTC enrolled in a multicenter, open-label, multi-cohort clinical trial (NCT03157128). The study enrolled patients with advanced or metastatic *RET*-mutant MTC who had been previously treated with cabozantinib or vandetanib (or both) and patients with advanced or metastatic *RET*-mutant MTC who were naïve to cabozantinib and vandetanib in separate cohorts.

RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib

Efficacy was evaluated in 55 patients with *RET*-mutant advanced MTC who had previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.

The median age was 57 years (range: 17 to 84); 66% were male; 89% were White, 7% were Hispanic/Latino, and 1.8% were Black. ECOG performance status was 0-1 (95%) or 2 (5%) and 98% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range 1 – 8). *RET* mutation status was detected in 82% of patients using NGS (78% tumor samples; 4% blood or plasma), 16% using PCR, and 2% using an unknown test. The protocol excluded patients with synonymous, frameshift or nonsense *RET* mutations; the specific mutations used to identify and enroll patients are described in Table 18.

Table 18: Mutations used to Identify and Enroll Patients with RET-Mutant MTC in LIBRETTO-001

RET Mutation Type[1]	Previously Treated (n = 55)	Cabozantinib/ Vandetanib Naïve (n = 88)	Total (n = 143)
M918T	33	49	82
Extracellular cysteine mutation[2]	7	20	27
V804M or V804L	5[4]	6	11
Other[3]	10	13	23

1 Somatic or germline mutations; protein change.

2 Extracellular cysteine mutations involving cysteine residues 609, 611, 618, 620, 630, and 634.

3 Other included: K666N (1), D631_L633delinsV (2), D631_L633delinsE (5), D378_G385delinsE (1), D898_E901del (2), A883F (4), E632_L633del (4), L790F (2), T636_V637insCRT(1), D898_E901del + D903_S904delinsEP (1).

4 One patient also had a M918T mutation.

Efficacy results for *RET*-mutant MTC are summarized in Table 19.

Table 19: Efficacy Results in LIBRETTO-001 (*RET*-Mutant MTC Previously Treated with Cabozantinib or Vandetanib)

	RETEVMO (n = 55)
Overall Response Rate[1] (95% CI)	76% (63%, 87%)
Complete response	18%
Partial response	58%
Duration of Response	
Median in months (95% CI)	45.3 (29.9, NE)
% with ≥ 12 months[2]	76%

1 Confirmed overall response rate assessed by BIRC.

2 Based on observed duration of response.

NE = not estimable

Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC

Efficacy was evaluated in 88 patients with *RET*-mutant MTC who were cabozantinib and vandetanib treatment-naïve enrolled into a cohort of LIBRETTO-001.

The median age was 58 years (range: 15 to 82) with two patients (2.3%) aged 12 to 16 years; 66% were male; and 86% were White, 4.5% were Asian, and 2.3% were Hispanic/Latino. ECOG performance status was 0-1 (97%) or 2 (3.4%). All patients (100%) had metastatic disease and 18% had received 1 or 2 prior systemic therapies (including 8% kinase inhibitors, 4.5% chemotherapy, 2.3% anti-PD1/PD-L1 therapy, and 1.1% radioactive iodine). *RET* mutation status was detected in 77.3% of patients using NGS (75.0% tumor samples; 2.3% blood samples), 18.2% using PCR, and 4.5% using an unknown test. The mutations used to identify and enroll patients are described in Table 18.

Efficacy results for cabozantinib and vandetanib-naïve *RET*-mutant MTC are summarized in Table 20.

Table 20: Efficacy Results in LIBRETTO-001 (Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC)

	RETEVMO (n = 88)
Overall Response Rate[1] (95% CI)	81% (71%, 88%)
Complete response	28%
Partial response	52%

Duration of Response	
Median in months (95% CI)	NR (51.3, NE)
% with ≥ 12 months[2]	90%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NR = not reached, NE = not estimable

LIBRETTO-531

LIBRETTO-531 was a randomized (2:1), multicenter, open-label study (NCT04211337) in adults and adolescents with advance or metastatic *RET*-mutant MTC. The study evaluated the efficacy of RETEVMO versus physicians' choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant medullary thyroid cancer.

Patients were randomized to receive either RETEVMO (160 mg twice daily) or physicians' choice of cabozantinib (140 mg once daily) or vandetanib (300 mg once daily). Patients were stratified based on *RET* mutation (M918T vs. other) and intended treatment if randomized to the control arm (cabozantinib vs. vandetanib). The primary outcome was progression-free survival (PFS), as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

The median age was 55 years (range: 12 to 84), 63% were male, 58% were White, 23% were Asian, 2.4% were Black or African American, and 17% had unknown race. ECOG performance status was 0-1 (98%) or 2 (1.0%) with 0.7% unknown status. 77% of patients had metastatic disease and 6 patients (2.1%) had received 1 prior systemic therapy. *RET* mutation status was detected in 90% of patients using NGS (89% tumor samples; 8% blood or plasma), and 10% using PCR. Of patients enrolled in LIBRETTO-531, 63% had M918T *RET* mutations and 37% had other *RET* mutations.

Efficacy results for LIBRETTO-531 based on the preplanned interim efficacy analysis are provided in Table 21 and Figure 2. At the time of this analysis, overall survival data were immature with 18 deaths observed (14% of pre-specified events).

Table 21: Efficacy Results in LIBRETTO-531: RETEVMO versus Cabozantinib or Vandetanib

	RETEVMO N = 193	**Cabozantinib or Vandetanib N = 98**
PFS		
Number (%) of patients with an event	26 (14%)	33 (34%)
Median in months (95% CI)	NR (NE, NE)	16.8 (12.2, 25.1)
Hazard ratio (95% CI)1	0.280 (95% CI: 0.165, 0.475)	
p-value2	<0.0001	
Overall Response Rate		
ORR (95% CI)	69% (62%, 76%)	39% (29%, 49%)
Complete response	12%	4%
Partial response	58%	35%
Duration of Response		
Median in months (95% CI)	NR (NE, NE)	16.6 (10.4, NE)
Median follow-up time (months)	11.1	12.8

Data from the pre-planned interim efficacy analysis.

[1] Based on the stratified Cox proportional hazard model.

[2] Based on stratified log-rank test.

NR = Not reached; NE = not evaluable

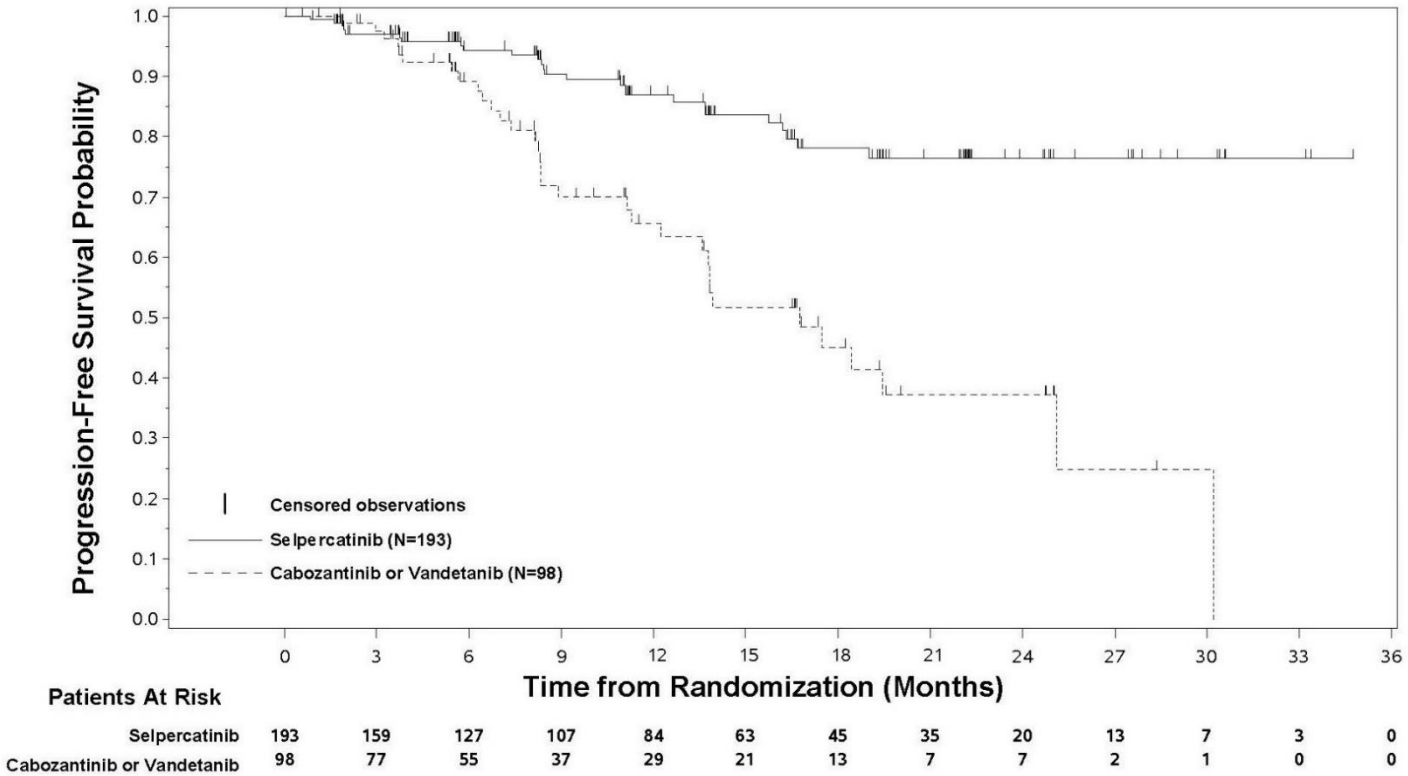


Figure 2: Kaplan-Meier Curves of Progression-Free Survival in LIBRETTO-531: RETEVMO versus Cabozantinib or Vandetanib

Patient-reported overall side effect impact was evaluated weekly in 222 patients (RETEVMO N = 145; cabozantinib or vandetanib N=77) who received at least one dose of treatment by at least 6 months prior to the data cutoff date and responded to the Functional Assessment of Cancer Therapy item GP5 (FACT GP5). Patient-reported overall side effect impact was derived as a proportion of time on treatment with high side effect bother (defined as response of 3 “Quite a bit” or 4 “Very much”) per FACT GP5.

Patient-reported overall side effect impact results for LIBRETTO-531 are provided in Table 22.

Table 22. Descriptive Summary of Patient-reported Overall Side Effect Impact While on Treatment in LIBRETTO-531

	RETEVMO (N=145)	**Cabozantinib or Vandetanib (N=77)**
Mean proportion of time with high side effect bother (95% CI)	8% (4.8%, 10%)	24% (17%, 31%)
% Patients with high side effect bother 0% of time ≤25% of time	61% 90%	30% 66%

Patient-reported overall side effect impact results were supported by a lower incidence of treatment discontinuation due to adverse reactions for RETEVMO (4.7%) compared to cabozantinib or vandetanib (27%) in patients who received at least one dose of study treatment. The median time on treatment at the data cutoff was 14.5 months in the RETEVMO arm and 8.3 months in the cabozantinib or vandetanib arm in patients who received at least one dose of study treatment.

LIBRETTO-121

The efficacy of RETEVMO was evaluated in pediatric and young adult patients with advanced *RET*-activated solid tumors enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-121**,** NCT03899792). Patients received RETEVMO 92 mg/m^2 orally twice daily until disease progression, unacceptable toxicity, or other reason for treatment

discontinuation. Tumor assessments were performed every 8 weeks for one year, then every 12 weeks; responses were assessed according to RECIST 1.1 per BIRC.

Efficacy was evaluated in 14 patients with *RET*-mutant MTC who were non-responsive to available therapies or had no standard systemic curative therapy available. The median age was 14 years (range 2 to 20); 64% were male; 71% were White, 14% were Black or African American; and 14% were Hispanic/Latino. Patients had metastatic (71%) or locally advanced (29%) disease; 43% had measurable disease at baseline; 21% had received prior systemic therapy. *RET*-mutant status was detected in 79% of patients using NGS tumor samples and in 21% using PCR.

Efficacy results for *RET*-mutant MTC in pediatric and young adult patients are summarized in Table 23.

Table 23: Efficacy Results in LIBRETTO-121 (*RET*-Mutant MTC)

	RETEVMO (n = 14)
Overall Response Rate[1] (95% CI)	57% (29, 82)
Complete response	36%
Partial response	21%
Duration of Response	
Median in months (range)	Not reached (8.3+, 49.7+)
% with ≥ 18 months[2]	88%
% with ≥ 24 months[2]	75%

1 Confirmed overall response rate assessed by BIRC.

2 Based on observed duration of response.

\+ Denotes ongoing response.

14.3 *RET* Fusion-Positive Thyroid Cancer

LIBRETTO-001

The efficacy of RETEVMO was evaluated in patients with advanced *RET* fusion-positive thyroid cancer enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). Efficacy was evaluated in 65 patients with *RET* fusion-positive thyroid cancer who were radioactive iodine (RAI)-refractory (if RAI was an appropriate treatment option) and were systemic therapy naïve and patients who were previously treated, in separate cohorts.

The median age was 59 years (range 20 to 88); 49% were male; 65% were White, 20% were Asian, 4.6% were Black or African American; and 11% were Hispanic/Latino. ECOG performance status was 0-1 (94%) or 2 (6%). All (100%) patients had metastatic disease with primary tumor histologies including papillary thyroid cancer (83%), poorly differentiated thyroid cancer (9%), anaplastic thyroid cancer (6%) and Hurthle cell thyroid cancer (1.5%). Previously treated patients had received a median of 1 prior therapy (range 1–4). *RET* fusion-positive status was detected in 97% of patients using NGS (89% tumor samples; 8% blood or plasma samples), and 3% using other local testing methods.

Efficacy results for *RET* fusion-positive thyroid cancer are summarized in Table 24.

Table 24: Efficacy Results in LIBRETTO-001 (*RET* Fusion-Positive Thyroid Cancer)

	RETEVMO Previously Treated (n = 41)	**RETEVMO Systemic Therapy Naïve (n = 24)**
Overall Response Rate[1] (95% CI)	85% (71%, 94%)	96% (79%, 100%)
Complete response	12%	21%
Partial response	73%	75%
Duration of Response		
Median in months (95% CI)	26.7 (12.1, NE)	NE (42.8, NE)
% with ≥ 12 months[2]	54	65

1 Confirmed overall response rate assessed by BIRC.

2 Based on observed duration of response.

NE = not estimable

Responses were observed in patients with each histology represented, including 3 of 4 patients with anaplastic thyroid cancer (all partial responses) and 6 of 6 patients with poorly differentiated thyroid cancer (1 complete response, 5 partial responses).

LIBRETTO-121

The efficacy of RETEVMO was evaluated in pediatric and young adult patients with advanced *RET*-activated solid tumors enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-121**,** NCT03899792) *[see Clinical Studies (14.2)].*

Efficacy was evaluated in 15 patients with *RET* fusion-positive thyroid cancer who were non-responsive to available therapies or had no standard systemic curative therapy available. The median age was 12 years (range 6 to 20); 53% were male; 40% were White, 47% were Asian, 13% were other races; and 27% were Hispanic/Latino Patients had metastatic (87%) or locally advanced (13%) disease and 100% had papillary thyroid cancer histology; 47% had measurable disease at baseline; 20% had received prior systemic therapy. *RET* fusion-positive status was detected in 93% of patients using NGS tumor samples and in 7% using FISH. Efficacy results for *RET* fusion-positive thyroid cancer in pediatric and young adult patients are summarized in Table 25.

Table 25: Efficacy Results in LIBRETTO-121 (*RET* Fusion-Positive Thyroid Cancer)

	RETEVMO (n = 15)
Overall Response Rate[1] (95% CI)	53% (27, 79)
Complete response	27%
Partial response	27%
Duration of Response	
Median in months (range)	Not reached (12.9+, 44.2)
% with ≥ 18 months[2]	88%
% with ≥ 24 months[2]	75%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

\+ Denotes ongoing response.

14.4 Other *RET* Fusion-Positive Solid Tumors

LIBRETTO-001

The efficacy of RETEVMO was evaluated in patients with locally advanced or metastatic *RET* fusion-positive solid tumors enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). Efficacy was evaluated in 41 patients with *RET* fusion-positive tumors other than NSCLC and thyroid cancer with disease progression on or following prior systemic treatment or who had no satisfactory alternative treatment options.

The median age was 50 years (range 21 to 85), 54% were female, 68% were White, 24% were Asian, and 4.9% were Black; and 7% were Hispanic/Latino. ECOG performance status was 0-1 (95%) or 2 (5%) and 95% of patients had metastatic disease. Thirty-seven patients (90%) received prior systemic therapy (median 2 [range 0 – 9]; 32% received 3 or more). The most common cancers were pancreatic adenocarcinoma (27%), colorectal (24%), salivary (10%) and unknown primary (7%). *RET* fusion-positive status was detected in 97.6% of patients using NGS and 2.4% using FISH.

Efficacy results for *RET* fusion-positive solid tumors other than NSCLC and thyroid cancer are summarized in Table 26 and Table 27.

Table 26: Efficacy Results in LIBRETTO-001 (Other *RET* Fusion-Positive Solid Tumors)

	RETEVMO (n = 41)
Overall Response Rate[1] (95% CI)	44% (28, 60)
Complete response	4.9%

Partial response	39%
Duration of Response	
Median in months (95% CI)	24.5 (9.2, NE)
% with ≥6 months[2]	67%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

Table 27: Efficacy Results by Tumor Type in LIBRETTO-001 (Other *RET* Fusion-Positive Solid Tumors)

Tumor Type	Patients (n = 41)	ORR[1,2]		DOR Range (months)
		n (%)	95% CI	
Pancreatic adenocarcinoma	11	6 (55%)	(23, 83)	2.5, 38.3+
Colorectal	10	2 (20%)	(2.5, 56)	5.6, 13.3
Salivary	4	2 (50%)	(7, 93)	5.7, 28.8+
Unknown primary	3	1 (33%)	(0.8, 91)	9.2
Breast	2	PR, CR	NA	2.3+, 17.3
Sarcoma (soft tissue)	2	PR, SD	NA	14.9+
Xanthogranuloma	2	NE, NE	NA	NA
Carcinoid (bronchial)	1	PR	NA	24.1+
Carcinoma of the skin	1	NE	NA	NA
Cholangiocarcinoma	1	PR	NA	5.6+
Ovarian	1	PR	NA	14.5+
Pulmonary carcinosarcoma	1	NE	NA	NA
Rectal neuroendocrine	1	NE	NA	NA
Small intestine	1	CR	NA	24.5

\+ denotes ongoing response.

[1] Confirmed overall response rate assessed by BIRC.

[2] Best overall response for each patient is presented for tumor types with ≤2 patients.

CI = confidence interval, CR = complete response, DOR = duration of response, NA = not applicable, NE = not evaluable, ORR = overall response rate, PR = partial response, SD = stable disease.

LIBRETTO-121

The efficacy of RETEVMO was evaluated in pediatric and young adult patients with advanced *RET*-activated solid tumors enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-121**,** NCT03899792) *[see Clinical Studies (14.2)].*

Efficacy was evaluated in 3 patients with locally advanced refractory *RET*-fusion positive other solid tumors who were unresponsive to available therapies or had no standard systemic curative therapy available. The median age was 15 years (range 6 to 15). One patient with congenital infantile fibrosarcoma and one patient with a spindle cell sarcoma had a partial response. One patient with malignant peripheral nerve sheath tumor did not respond. Responses were observed in patients with *RET* fusion-positive thyroid cancer *[see Clinical Studies (14.3)].*

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

RETEVMO capsules are supplied as follows:

Capsule Strength	Description	Package Configuration	NDC Number
40 mg	Gray opaque, imprinted with “Lilly”, “3977” and “40 mg” in black ink	60 count bottle	NDC 0002-3977-60
80 mg	Blue opaque, imprinted with “Lilly”, “2980” and “80 mg” in black ink	60 count bottle	NDC 0002-2980-60
		120 count bottle	NDC 0002-2980-26

RETEVMO tablets are supplied in bottles with desiccant in the following configurations:

Tablet Strength	Description	Package Configuration	NDC Number
40 mg	Light gray, film coated, round tablets debossed with “Ret 40” on one side and “5340” on the other side	60 count bottle	NDC 0002-5340-60
80 mg	Dark red-purple, film coated, round tablets debossed with “Ret 80” on one side and ”6082” on the other side	60 count bottle	NDC 0002-6082-60
120 mg	Light purple, film coated, round tablets debossed with “Ret 120” on one side and “6120” on the other side	60 count bottle	NDC 0002-6120-60
160 mg	Light pink, film coated, round tablets debossed with Ret “160” on one side and “5562” on the other side	60 count bottle	NDC 0002-5562-60

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions between 15°C and 30°C (59°F to 86°F) are permitted [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hepatotoxicity

Advise patients that hepatotoxicity can occur and to immediately contact their healthcare provider for signs or symptoms of hepatotoxicity *[see Warnings and Precautions (5.1)]*.

Interstitial Lung Disease (ILD)/Pneumonitis

Advise patients that ILD/ pneumonitis can occur and to contact their healthcare provider immediately for signs or symptoms of ILD including new or worsening cough or shortness of breath *[see Warnings and Precautions (5.2)].*

Hypertension

Advise patients that they will require regular blood pressure monitoring and to contact their healthcare provider if they experience symptoms of increased blood pressure or elevated readings *[see Warnings and Precautions (5.3)]*.

QT Prolongation

Advise patients that RETEVMO can cause QTc interval prolongation and to inform their healthcare provider if they have any QTc interval prolongation symptoms, such as syncope *[see Warnings and Precautions (5.4)]*.

Hemorrhagic Events

Advise patients that RETEVMO may increase the risk for bleeding and to contact their healthcare provider if they experience any signs or symptoms of bleeding [*see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

Advise patients to monitor for signs and symptoms of hypersensitivity reactions, particularly during the first month of treatment *[see Warnings and Precautions (5.6)]*.

Tumor Lysis Syndrome

Advise patients to contact their healthcare provider promptly to report any signs and symptoms of TLS *[see Warnings and Precautions (5.7)]*.

Risk of Impaired Wound Healing

Advise patients that RETEVMO may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure *[see Warnings and Precautions (5.8)]*.

Hypothyroidism

Advise patients that RETEVMO can cause hypothyroidism and to immediately contact their healthcare provider for signs or symptoms of hypothyroidism *[see Warnings and Precautions (5.9)]*.

Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis

Advise pediatric patients and caregivers to contact their healthcare provider promptly to report any signs and symptoms indicative of slipped capital femoral epiphysis/slipped upper femoral epiphysis *[see Warnings and Precautions (5.11)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the possible risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during the treatment with RETEVMO and for 1 week after the last dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with RETEVMO and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males and females of reproductive potential that RETEVMO may impair fertility *[see Use in Specific Populations (8.4), Nonclinical Toxicology (13.1)]*.

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John’s wort, proton pump inhibitors, H2 receptor antagonists, and antacids while taking RETEVMO.

If PPIs are required, instruct patients to take RETEVMO with food. If H2 receptor antagonists are required, instruct patients to take RETEVMO 2 hours before or 10 hours after the H2 receptor antagonist. If locally-acting antacids are required, instruct patients to take RETEVMO 2 hours before or 2 hours after the locally-acting antacid *[see Drug Interactions (7.1, 7.2)]*.

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RET-0009-USPI-20251120

ANNEX I

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 40 mg hard capsules
Retsevmo 80 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Retsevmo 40 mg hard capsules

Each hard capsule contains 40 mg selpercatinib.

Retsevmo 80 mg hard capsules

Each hard capsule contains 80 mg selpercatinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Retsevmo 40 mg hard capsules

Grey opaque capsule, 6 x 18 mm (size 2), imprinted with “Lilly”, “3977” and “40 mg” in black ink.

Retsevmo 80 mg hard capsules

Blue opaque capsule, 8 x 22 mm (size 0), imprinted with “Lilly”, “2980” and “80 mg” in black ink.

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

– advanced *RET* fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted (see sections 4.4 and 5.1)

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 mutation (MTC) or fusion (all other tumour types) 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 tumours except RET fusion-positive thyroid cancer.

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 capsules should be swallowed whole (patients should not open, crush, or chew the capsule before swallowing) and can be taken with or without food.
Patients should take the doses at approximately the same 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

Efficacy across tumour types

The benefit of selpercatinib has been established in single arm trials encompassing a relatively small sample of patients whose tumours exhibit RET gene fusions. Favourable effects of selpercatinib have been shown on the basis of objective response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on tumour type, as well as on concomitant genomic alterations (see section 5.1). For these reasons, selpercatinib should only be used if there are no treatment options for which clinical benefit has been established, or where such treatment options have been exhausted (i.e., no satisfactory treatment options).

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.

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 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) (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

MedDRA system organ class	MedDRA preferred term	Frequency of all Grades	Frequency of Grade ≥ 3
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
	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 national reporting system listed in Appendix V.

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, RET fusion-positive thyroid cancer, other RET fusion-positive solid tumours, 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.

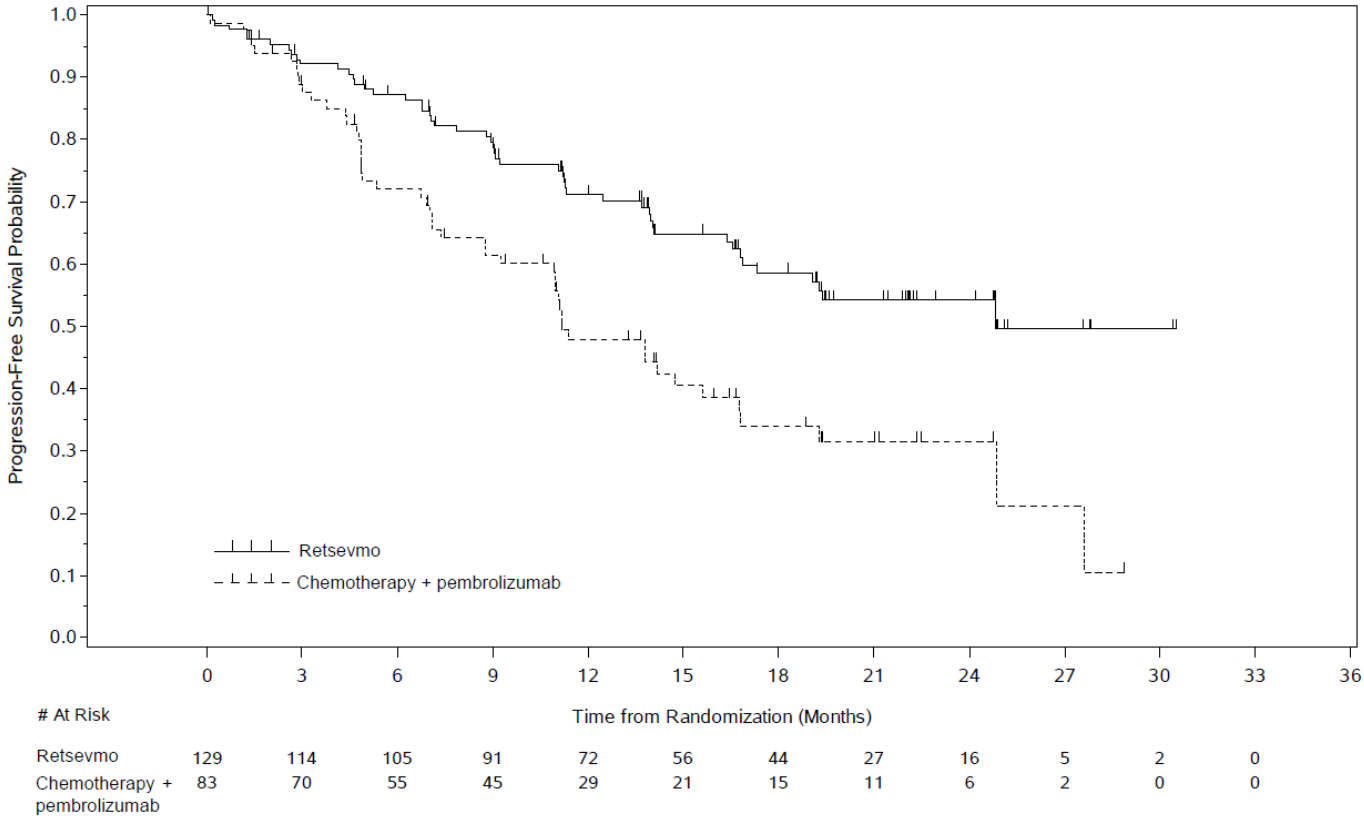
Table 4 LIBRETTO-431: Summary of efficacy data (BICR assessment, ITT-Pembrolizumab population)

	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, CR = complete response, NE = not estimable, 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	
≥ 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.

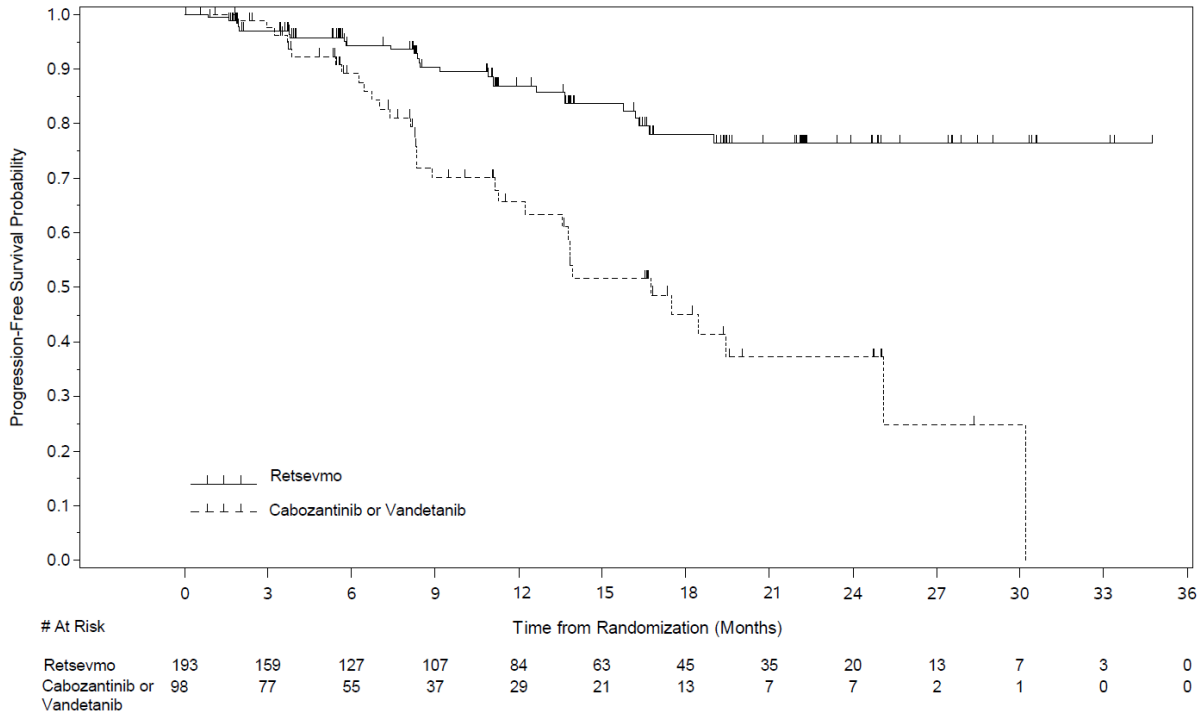
Of the 291 patients enrolled and randomised in LIBRETTO-531 to form the ITT population, 193 were randomised to the selpercatinib arm, and 98 were randomised to the control arm. Of the 98 patients randomised to the control arm, 73 were stratified to cabozantinib, and 25 were stratified to vandetanib. 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 (25th, 75th percentile: 5.62, 16.62) in the selpercatinib arm and 12.81 months (25th and 75th 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 (25th, 75th percentile: 23.0, 46.1).
Data cut-off date 13 January 2023.

Other RET Fusion-Positive Solid Tumours

Efficacy was evaluated in 75 patients with *RET* fusion-positive tumours other than NSCLC and thyroid cancer with disease progression on or following prior systemic treatment or who had no satisfactory alternative treatment options. The median age was 59 years (range 21 to 92); 50.7% were female; 60.0% were White, 34.7% were Asian, and 4.0% were Black; ECOG performance status was 0-1 (90.6%) or 2 (9.3%) and 96.0% of patients had metastatic disease. Sixty-nine patients (92.0%) received prior systemic therapy with a median of 2 prior systemic therapies (range 0 to 9) and 36.0% received 3 or more prior systemic therapies. No patients had been previously treated with a selective RET inhibitor. The most common cancers were colon (29.3%), pancreatic (24.0%), salivary (6.7%), sarcoma (6.7%) and cholangiocarcinoma (6.7%). The most common fusion partners were NCOA4 (38.7%), CCDC6 (20.0%), and KIF5B (8.0%). Efficacy results for *RET* fusion-positive solid tumours other than NSCLC and thyroid cancer are summarized in Table 12 and Table 13.

Table 12 LIBRETTO-001: Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	75
Objective response (CR+PR)	
% (95% CI)	46.7 (35.1, 58.6)
Complete response n (%)	4 (5.3)
Partial response n (%)	31 (41.3)
Duration of Response (months)*	
Median (95% CI)	24.54 (11.2, 49.1)
Rate (%) of duration of response	
≥ 6 months (95% CI)	82.0 (64.2, 91.5)
≥ 12 months (95% CI)	68.6 (49.3, 81.8)
≥ 24 months (95% CI)	52.5 (32.6, 69.0)
≥ 36 months (95% CI)	43.3 (24.0, 61.1)

*Median duration of follow-up was 32.23 months (25th, 75th percentile: 13.3, 50.8)
CI = Confidence Interval, CR = complete response, NE = not estimable, PR = partial response
Data cut-off date 14 February 2025

Table 13 LIBRETTO-001: Objective response and duration of response by Tumour Type

Tumour Type	Patients (N = 75)	ORR (IRC assessment)		DOR
		n (%)	95% CI	Range (months)
Colorectal	22	10 (45.5)	24.4, 67.8	4.63, 36.14+
Pancreatic	18	9 (50.0)	26.0, 74.0	2.50, 52.14
Salivary	5	3 (60.0)	14.7, 94.7	5.72, 37.19
Cholangiocarcinoma	5	2 (40.0)	5.3, 85.3	7.36, 14.82
Sarcoma	5	2 (40.0)	5.3, 85.3	3.71, 56.51+
Carcinoma of the skin	3	1 (33.3)	0.8, 90.6	27.14
Unknown primary	3	1 (33.3)	0.8, 90.6	9.23
Breast	2	PR, CR	15.8, 100.0	2.30+, 17.28
Xanthogranuloma	2	NE, NE [a]	0.0, 84.2	NA
Carcinoid	1	PR	2.5, 100.0	49.08
Ovarian	1	PR	2.5, 100.0	28.55+
Pulmonary carcinosarcoma	1	NE	0.0, 97.5	NA
Rectal neuroendocrine	1	NE	0.0, 97.5	NA
Small intestine	1	CR	2.5, 100.0	24.54
Neuroendocrine	1	PR	2.5, 100.0	23.13
Small cell lung cancer	1	SD	0.0, 97.5	NA
Gastroesophageal junction	1	SD	0.0, 97.5	NA
Pancreatic neuroendocrine	1	PR	2.5, 100.0	17.51+
Stomach	1	SD	0.0, 97.5	NA

+ denotes ongoing response.

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

CI = confidence interval, CR = complete response, DOR = duration of response, NA = not applicable, NE = not evaluable, ORR = objective response rate, PR = partial response, SD = stable disease.
Data cut-off date 14 February 2025

Due to the rarity of RET fusion-positive cancer, patients were studied across multiple tumour types with a limited number of patients in some tumour types, causing uncertainty in the ORR estimate per tumour type. The ORR in the total population may not reflect the expected response in a specific tumour type.

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 European Medicines 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 European Medicines Agency 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 European Medicines Agency 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

Capsule content

Cellulose, microcrystalline
Silica, colloidal anhydrous

Capsule shell

Retsevmo 40 mg hard capsules
Gelatin
Titanium dioxide (E171)
Iron Oxide (E172)

Retsevmo 80 mg hard capsules
Gelatin
Titanium dioxide (E171)
Brilliant Blue FCF (E133)

Capsules black ink composition

Shellac
Ethanol (96 per cent),
Isopropyl alcohol
Butanol
Propylene glycol
Water, purified
Ammonia solution, concentrated
Potassium hydroxide
Iron oxide black

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

Plastic bottle

Each pack contains 1 HDPE bottle with a plastic screw cap.

Retsevmo 40 mg hard capsules
Retsevmo 40 mg hard capsules is supplied as a 60 count HDPE bottle.

Retsevmo 80 mg hard capsules
Retsevmo 80 mg hard capsules is supplied as 60 count HDPE bottle or 120 count HDPE bottle.

Blister pack

Retsevmo 40 mg hard capsules
Supplied as PCTFE/PVC blisters sealed with an aluminium foil in a blister card, in packs of 14, 42, 56 or 168 hard capsules.

Retsevmo 80 mg hard capsules
Supplied as PCTFE/PVC blisters sealed with an aluminium foil in a blister card, in packs of 14, 28, 56 or 112 hard capsules.

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)

EU/1/20/1527/001
EU/1/20/1527/002
EU/1/20/1527/003
EU/1/20/1527/004
EU/1/20/1527/005
EU/1/20/1527/006
EU/1/20/1527/007
EU/1/20/1527/008
EU/1/20/1527/009
EU/1/20/1527/010
EU/1/20/1527/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 February 2021
Date of latest renewal: 12 December 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

▼ 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 40 mg film-coated tablets
Retsevmo 80 mg film-coated tablets
Retsevmo 120 mg film-coated tablets
Retsevmo 160 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.

Retsevmo 120 mg film-coated tablets

Each film-coated tablet contains 120 mg selpercatinib.

Retsevmo 160 mg film-coated tablets

Each film-coated tablet contains 160 mg selpercatinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Retsevmo 40 mg film-coated tablets

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

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.

Retsevmo 120 mg 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.

Retsevmo 160 mg 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

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

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

– advanced *RET* fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted (see sections 4.4 and 5.1)

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 mutation (MTC) or fusion (all other tumour types) 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 tumours except RET fusion-positive thyroid cancer.
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

Efficacy across tumour types

The benefit of selpercatinib has been established in single arm trials encompassing a relatively small sample of patients whose tumours exhibit RET gene fusions. Favourable effects of selpercatinib have been shown on the basis of objective response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on tumour type, as well as on concomitant genomic alterations (see section 5.1). For these reasons, selpercatinib should only be used if there are no treatment options for which clinical benefit has been established, or where such treatment options have been exhausted (i.e., no satisfactory treatment options).

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-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-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

MedDRA system organ class	MedDRA preferred term	Frequency of all Grades	Frequency of Grade ≥ 3
	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
	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 national reporting system listed in Appendix V.

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, RET fusion-positive thyroid cancer, other RET fusion-positive solid tumours, 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).

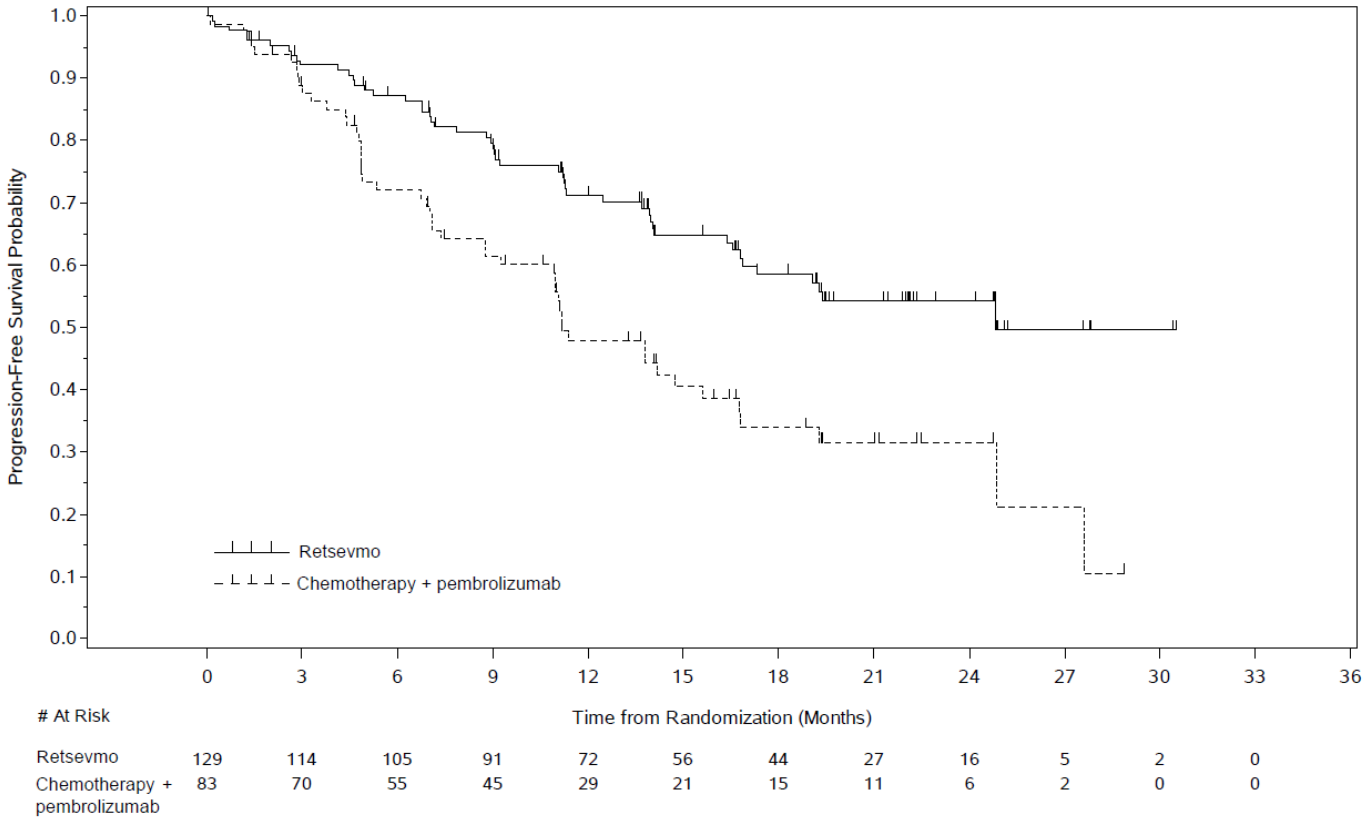
Of the 261 patients enrolled and randomized in Study LIBRETTO-431 intention to treat (ITT) population, 212 were stratified according to whether the investigator would intend for the patient to receive pembrolizumab (before randomisation), to form the ITT-Pembrolizumab population. In the ITT-Pembrolizumab 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 (25th, 75th percentile: 12.32, 21.03) in the selpercatinib arm and 14.55 months (25th, 75th 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	
≥ 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 (25th, 75th 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 (25th, 75th 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.

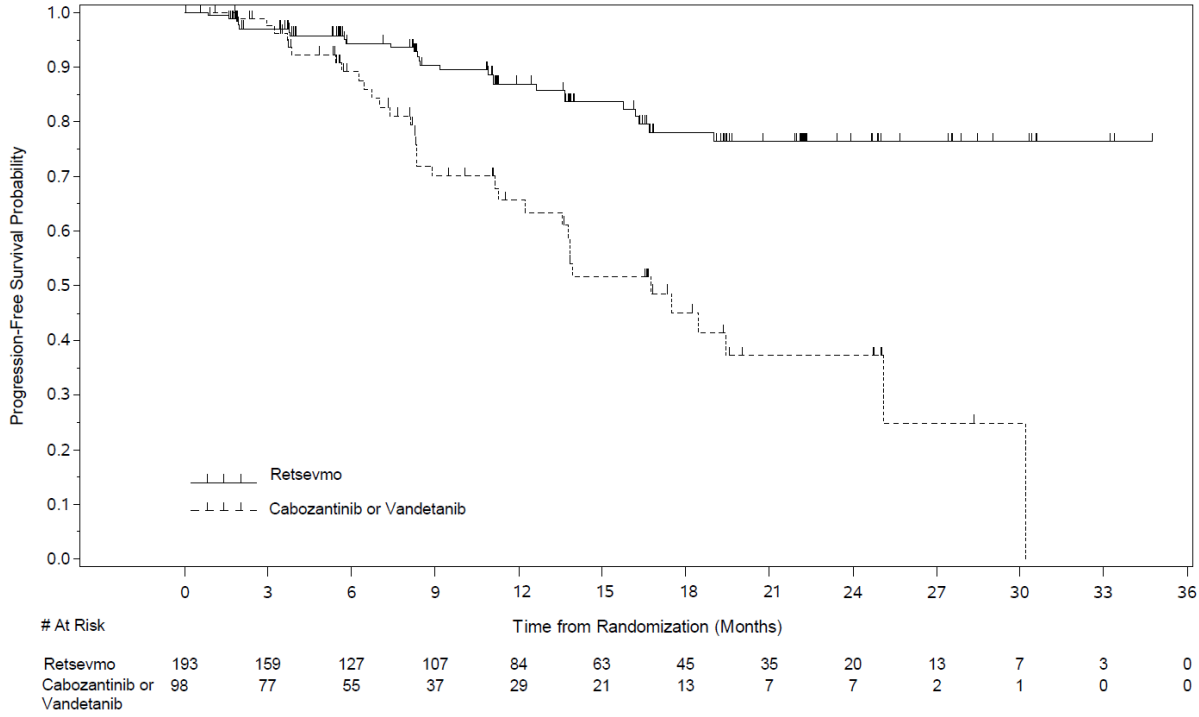
Of the 291 patients enrolled and randomised in LIBRETTO-531 to form the ITT population, 193 were randomised to the selpercatinib arm, and 98 were randomised to the control arm. Of the 98 patients randomised to the control arm, 73 were stratified to cabozantinib, and 25 were stratified to vandetanib.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

Other RET Fusion-Positive Solid Tumours

Efficacy was evaluated in 75 patients with *RET* fusion-positive tumours other than NSCLC and thyroid cancer with disease progression on or following prior systemic treatment or who had no satisfactory alternative treatment options. The median age was 59 years (range 21 to 92); 50.7% were female; 60.0% were White, 34.7% were Asian, and 4.0% were Black; ECOG performance status was 0-1 (90.6%) or 2 (9.3%) and 96.0% of patients had metastatic disease. Sixty-nine patients (92.0%) received prior systemic therapy with a median of 2 prior systemic therapies (range 0 to 9) and 36.0%

received 3 or more prior systemic therapies. No patients had been previously treated with a selective RET inhibitor. The most common cancers were colon (29.3%), pancreatic (24.0%), salivary (6.7%), sarcoma (6.7%) and cholangiocarcinoma (6.7%). The most common fusion partners were NCOA4 (38.7%), CCDC6 (20.0%), and KIF5B (8.0%). Efficacy results for *RET* fusion-positive solid tumours other than NSCLC and thyroid cancer are summarized in Table 12 and Table 13.

Table 12 LIBRETTO-001: Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	75
Objective response (CR+PR)	
% (95% CI)	46.7 (35.1, 58.6)
Complete response n (%)	4 (5.3)
Partial response n (%)	31 (41.3)
Duration of Response (months)*	
Median (95% CI)	24.54 (11.2, 49.1)
Rate (%) of duration of response	
≥ 6 months (95% CI)	82.0 (64.2, 91.5)
≥ 12 months (95% CI)	68.6 (49.3, 81.8)
≥ 24 months (95% CI)	52.5 (32.6, 69.0)
≥ 36 months (95% CI)	43.3 (24.0, 61.1)

*Median duration of follow-up was 32.23 months (25th, 75th percentile: 13.3, 50.8)
CI = Confidence Interval, CR = complete response, NE = not estimable, PR = partial response
Data cut-off date 14 February 2025

Table 13 LIBRETTO-001: Objective response and duration of response by Tumour Type

Tumour Type	**Patients (N = 75)**	**ORR (IRC assessment)**		**DOR**
		n (%)	**95% CI**	**Range (months)**
Colorectal	22	10 (45.5)	24.4, 67.8	4.63, 36.14+
Pancreatic	18	9 (50.0)	26.0, 74.0	2.50, 52.14
Salivary	5	3 (60.0)	14.7, 94.7	5.72, 37.19
Cholangiocarcinoma	5	2 (40.0)	5.3, 85.3	7.36, 14.82
Sarcoma	5	2 (40.0)	5.3, 85.3	3.71, 56.51+
Carcinoma of the skin	3	1 (33.3)	0.8, 90.6	27.14
Unknown primary	3	1 (33.3)	0.8, 90.6	9.23
Breast	2	PR, CR	15.8, 100.0	2.30+, 17.28
Xanthogranuloma	2	NE, NE [a]	0.0, 84.2	NA
Carcinoid	1	PR	2.5, 100.0	49.08
Ovarian	1	PR	2.5, 100.0	28.55+
Pulmonary carcinosarcoma	1	NE	0.0, 97.5	NA
Rectal neuroendocrine	1	NE	0.0, 97.5	NA
Small intestine	1	CR	2.5, 100.0	24.54
Neuroendocrine	1	PR	2.5, 100.0	23.13

Small cell lung cancer	1	SD	0.0, 97.5	NA
Gastroesophageal junction	1	SD	0.0, 97.5	NA
Pancreatic neuroendocrine	1	PR	2.5, 100.0	17.51+
Stomach	1	SD	0.0, 97.5	NA

+ denotes ongoing response.

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

CI = confidence interval, CR = complete response, DOR = duration of response, NA = not applicable, NE = not evaluable, ORR = objective response rate, PR = partial response, SD = stable disease.
Data cut-off date 14 February 2025

Due to the rarity of RET fusion-positive cancer, patients were studied across multiple tumour types with a limited number of patients in some tumour types, causing uncertainty in the ORR estimate per tumour type. The ORR in the total population may not reflect the expected response in a specific tumour type.

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 European Medicines 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 European Medicines Agency 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 European Medicines Agency 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)

Retsevmo 120 mg film-coated tablets
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Black iron oxide (E172)
Red iron oxide (E172)

Retsevmo 160 mg film-coated tablets
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Red 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)

EU/1/20/1527/012
EU/1/20/1527/013
EU/1/20/1527/014
EU/1/20/1527/015
EU/1/20/1527/016
EU/1/20/1527/017
EU/1/20/1527/018
EU/1/20/1527/019
EU/1/20/1527/020
EU/1/20/1527/021
EU/1/20/1527/022
EU/1/20/1527/023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 February 2021
Date of latest renewal: 12 December 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Lilly, S.A.
Avda. de la Industria, 30
28108 Alcobendas, Madrid
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

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

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

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

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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive thyroid cancer, the MAH should submit the final data from the study LIBRETTO-121.	30 June 2025

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PLASTIC BOTTLE - CARTONS FOR 40 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 40 mg hard capsules
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 40 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1527/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Retsevmo 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

PLASTIC BOTTLE - LABEL FOR 40 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 40 mg hard capsules
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 40 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If inner seal is broken, do not use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lilly logo

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1527/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER PACK - CARTONS FOR 40 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 40 mg hard capsules
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 40 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules
42 hard capsules
56 hard capsules
168 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1527/004 (14 hard capsules)
EU/1/20/1527/005 (42 hard capsules)
EU/1/20/1527/006 (56 hard capsules)
EU/1/20/1527/007 (168 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Retsevmo 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER PACK - BLISTER CARD FOR 40 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 40 mg hard capsules
selpercatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

morning

evening

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER PACK - BLISTER TO BE USED INSIDE THE BLISTER CARDS FOR 40 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 40 mg
selpercatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PLASTIC BOTTLE - CARTONS FOR 80 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 80 mg hard capsules
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 80 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules
120 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1527/002 (60 hard capsules)
EU/1/20/1527/003 (120 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Retsevmo 80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

PLASTIC BOTTLE - LABEL FOR 80 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 80 mg hard capsules
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 80 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules
120 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If inner seal is broken, do not use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lilly logo

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1527/002 (60 hard capsules)
EU/1/20/1527/003 (120 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER PACK - CARTONS FOR 80 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 80 mg hard capsules
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 80 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules
28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1527/008 (14 hard capsules)
EU/1/20/1527/009 (28 hard capsules)
EU/1/20/1527/010 (56 hard capsules)
EU/1/20/1527/011 (112 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Retsevmo 80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER PACK - BLISTER CARD FOR 80 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 80 mg hard capsules
selpercatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

morning

evening

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER PACK - BLISTER TO BE USED INSIDE THE BLISTER CARDS FOR 80 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 80 mg
selpercatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR 40 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 40 mg film-coated tablets
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 40 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
56 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1527/012 (30 film-coated tablets)
EU/1/20/1527/013 (56 film-coated tablets)
EU/1/20/1527/014 (60 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Retsevmo 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR 40 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 40 mg tablets
selpercatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR 80 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 80 mg film-coated tablets
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 80 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
56 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1527/015 (30 film-coated tablets)
EU/1/20/1527/016 (56 film-coated tablets)
EU/1/20/1527/017 (60 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Retsevmo 80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR 80 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 80 mg tablets
selpercatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR 120 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 120 mg film-coated tablets
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 120 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
56 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1527/018 (30 film-coated tablets)
EU/1/20/1527/019 (56 film-coated tablets)
EU/1/20/1527/020 (60 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Retsevmo 120 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR 120 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 120 mg tablets
selpercatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR 160 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 160 mg film-coated tablets
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 160 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
56 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1527/021 (30 film-coated tablets)
EU/1/20/1527/022 (56 film-coated tablets)
EU/1/20/1527/023 (60 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Retsevmo 160 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR 160 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 160 mg tablets
selpercatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Retsevmo 40 mg hard capsules
Retsevmo 80 mg hard capsules
selpercatinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- This leaflet has been written as though the person taking the medicine is reading it. If you are giving this medicine to your child, please replace "you" with "your child" throughout.

What is in this leaflet

1. What Retsevmo is and what it is used for
2. What you need to know before you take Retsevmo
3. How to take Retsevmo
4. Possible side effects
5. How to store Retsevmo
6. Contents of the pack and other information

1. What Retsevmo is and what it is used for

Retsevmo is an anticancer medicine containing the active substance selpercatinib.

It is used to treat the following cancers which are caused by certain abnormal changes in the RET gene and which have spread and/or cannot be removed by surgery:
- A type of lung cancer called non-small cell lung cancer, in adults who have not previously been treated with a *RET* inhibitor medicine.
- Thyroid cancer (any type) in adults and adolescents 12 years and older if radioactive iodine treatment, when appropriate, has failed to control your cancer.
- A rare type of thyroid cancer called medullary thyroid cancer in adults and adolescents 12 years and older.
- Solid tumours (cancer) in other parts of the body in adults after prior therapies have failed to control the cancer.

Your doctor will perform a test to check if your cancer has a change in the RET gene to make sure that Retsevmo is right for you.

How Retsevmo works
In patients whose cancer has an altered RET gene, the change in the gene causes the body to make an abnormal RET protein, which can lead to uncontrolled cell growth and cancer. Retsevmo blocks the action of the abnormal RET protein and so may slow or stop the growth of the cancer. It may also help to shrink the cancer.

If you have any questions about how Retsevmo works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take Retsevmo

Do not take Retsevmo
- if you are allergic to selpercatinib or any of the other ingredients of this medicine (listed in section 6).
- if you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking Retsevmo.

Warnings and precautions
Talk to your doctor before taking Retsevmo:
- If you have lung or breathing problems other than lung cancer.
- If you have high blood pressure.
- If you have been told that you have an abnormality of your heart tracing after an electrocardiogram (ECG) known as prolonged QT interval.
- If you have problems with your thyroid or levels of thyroid hormone.
- Retsevmo may affect fertility in females and males, which may affect your ability to have children. Talk to your doctor if this is a concern for you.
- If you have a recent history of significant bleeding.

Retsevmo may cause hypersensitivity reactions such as fever, rash and pain. If you experience any of these reactions, talk to your doctor. After checking your symptoms, your doctor may ask you to take corticosteroids until your symptoms are better.

A fast breakdown of cancer cells (tumour lysis syndrome, TLS) can occur when you are taking Retsevmo. This can cause irregular heartbeat, kidney failure or abnormal blood test results. Talk to your doctor if you have a history of kidney problems or low blood pressure, because this may increase the risks associated with TLS.

Retsevmo may cause irregular hip joint growth or damage in paediatric patients (<18 years of age). If you experience pain in the hip or knee or have an unexplained limp, talk to your doctor.

This medicine can cause serious skin reactions. Stop using Retsevmo and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

See section 4, “Possible side effects”, and talk to your doctor if you have any symptoms.

What your doctor will check before and during your treatment
- Retsevmo may cause severe, life-threatening, or fatal inflammation of the lungs. Your doctor will monitor you before and during treatment with Retsevmo for symptoms. Tell your doctor right away if you notice any symptoms of lung problems including breathlessness, cough and raised temperature.
- Retsevmo may affect your blood pressure. You will have your blood pressure measured before and during treatment with Retsevmo.
- Retsevmo may affect the way your liver works. Tell your doctor right away if you develop symptoms of liver problems including: jaundice (yellow discoloration of the skin and eyes), loss of appetite, nausea or vomiting, or pain on the upper right side of your stomach area.
- Retsevmo may result in abnormal ECGs. You will have an ECG taken before and during your treatment with Retsevmo. Tell your doctor if you experience fainting as it may be a symptom of abnormal ECG.
- Retsevmo may affect how your thyroid works. Your doctor will monitor your thyroid function before and during treatment with Retsevmo.
- You will have regular blood tests before and during treatment with Retsevmo, to check your liver function and electrolytes (such as sodium, potassium, magnesium and calcium) in your blood.

- If you are under 18 years of age, your doctor may monitor your growth during treatment. If you have hip, knee, or other leg pain let your doctor know.

Children and adolescents
Retsevmo is not intended for use in patients less than 18 years of age in lung cancer.
The thyroid cancer (including medullary thyroid cancer) indications do not cover children younger than 12 years of age.

Other medicines and Retsevmo
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or pharmacist before taking Retsevmo if you are taking the following:
- medicines that may increase the concentration of Retsevmo in the blood:
    - Clarithromycin (used to treat bacterial infections)
    - Itraconazole, ketoconazole, posaconazole, voriconazole (used to treat fungal infections)
    - Atazanavir, ritonavir, cobicistat (used to treat HIV infections/AIDS)
- medicines that may reduce the effectiveness of Retsevmo:
    - Carbamazepine (used to treat epilepsy, nerve pain, bipolar disorder)
    - Rifampicin (used to treat tuberculosis (TB) and some other infections)
    - St. John's wort (a herbal product used to treat mild depression and anxiety)
    - Omeprazole, lansoprazole, or other proton pump inhibitors used to treat heartburn, ulcers, and acid reflux. If you are taking any of these medicines, then take Retsevmo with a full meal
    - Ranitidine, famotidine or other H2 blockers used to treat ulcers and acid reflux. If you are taking any of these medicines, then you need to take them 2 hours after taking Retsevmo
- medicines whose concentration in the blood might be increased by Retsevmo:
    - Repaglinide (used to treat type 2 diabetes and control blood sugar)
    - Dasabuvir (used to treat hepatitis C)
    - Selexipag (used to treat pulmonary arterial hypertension)
    - Digoxin (used to treat heart disorders)
    - Lovastatin and simvastatin (used to treat high cholesterol)
    - Dabigatran (used to prevent and treat blood clots)
- medicines that may be less effective when taken with Retsevmo:
    - Levothyroxine (used to treat hypothyroidism)

Pregnancy, breast-feeding and fertility
Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor before taking this medicine.

You should not use Retsevmo during pregnancy, since the effect of Retsevmo on the unborn is not known.

Breast-feeding
Do not breast-feed during treatment with Retsevmo as Retsevmo could harm a breast-fed baby. It is not known if Retsevmo passes into breast milk. You should not breast-feed for at least one week after your last dose of Retsevmo.

Contraception
It is recommended that women avoid becoming pregnant and that men do not father children during treatment with Retsevmo, because this medicine could harm the baby. If there is any possibility that the person taking this medicine may become pregnant or father a child, they must use adequate contraception during treatment and for at least one week after the last dose of Retsevmo.

Fertility
Retsevmo can affect your ability to have children. Talk to your doctor to seek advice about fertility preservation prior to treatment.

Driving and using machines
You should take special care when driving and using machines as you may feel tired or dizzy while taking Retsevmo.

3. How to take Retsevmo

Always take this medicine exactly as your doctor or pharmacist has told you, at the dose prescribed for you. Check with your doctor or pharmacist if you are not sure.

How much to take
Your doctor will prescribe the right dose for you. The maximum recommended dose is as follows:

- Less than 50 kg body weight: 120 mg twice daily.

- 50 kg body weight or greater: 160 mg twice daily.

Retsevmo is taken twice a day at about the same time every day, preferably in the morning and evening.
If you get certain side effects while you are taking Retsevmo your doctor may lower your dose or stop treatment temporarily or permanently.

You can take the capsules either with or without food. Swallow the capsule whole with a glass of water. Do not chew, crush or split the capsule before swallowing.

Retsevmo is available in blister packs and in bottles. The bottle is protected by a plastic screw cap:

To open the bottle, push down the plastic screw cap while turning it anticlockwise as shown in the picture.



To close the bottle, turn the cap clockwise tightly.



If you take more Retsevmo than you should
If you take too many capsules, or if someone else takes your medicine, contact a doctor or hospital for advice. Medical treatment may be necessary.

If you forget to take Retsevmo
If you vomit after taking the dose or forget a dose, take your next dose at your usual time. Do not take a double dose to make up for the forgotten or vomited dose.

If you stop taking Retsevmo
Do not stop taking Retsevmo unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side-effects, although not everybody gets them.

Stop using Retsevmo and seek medical attention immediately if you notice any of the following symptoms of serious skin reactions:
- Reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms [Stevens-Johnson syndrome (SJS)].

Contact your doctor immediately for any of the following:
- Lung or breathing problems other than lung cancer with symptoms such as breathlessness, cough and raised temperature (which may affect more than 1 in 10 people)
- Liver problems (which may affect more than 1 in 10 people and can be associated with abnormalities in liver blood tests, such as increased liver enzymes) including: yellow discoloration of the skin and eyes (jaundice), darkening of the urine, loss of appetite, nausea or vomiting, or pain on the upper right side of your stomach area
- Allergic reaction typically shown by fever and muscle and joint pain followed by rash (which may affect up to 1 in 10 people)
- High blood pressure (which may affect more than 1 in 10 people)
- Bleeding with symptoms such as coughing up blood

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)
- Low blood levels of calcium
- Reduced number of white blood cells (e.g., lymphocytes, neutrophils, etc.)
- Low blood levels of albumin
- Fluid retention that may cause swelling in your hands or ankles (oedema)
- Diarrhoea
- Increased blood levels of creatinine in tests, which may indicate that kidneys are not working properly (renal disorders)
- Fatigue or tiredness
- Dry mouth
- Low blood levels of sodium
- Reduced number of blood platelets, which may cause bleeding and/or bruising
- Rash
- Pain in the belly
- Constipation
- Low levels of haemoglobin, which may cause anaemia
- Low blood levels of magnesium
- Nausea (feeling sick)
- Headache
- Vomiting
- Bleeding symptoms
- Impotence
- Decreased appetite
- Abnormal ECG
- Low blood levels of potassium
- Dizziness
- Infection of the urinary tract
- Fever or high temperature
- Inflammation of the mucous membrane of the mouth

- Reduced thyroid activity

Common (may affect more than 1 in 100 people)
- Lymph fluid may build up in the lining of your lungs or your stomach cavity, which may cause breathing problems or enlargement of the stomach
- Irregular hip joint growth or damage causing pain or limp in patients < 18 years of age

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Retsevmo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label or blister card and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the inner seal is broken or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Retsevmo contains
The active substance is selpercatinib. Each hard capsule contains 40 or 80 mg selpercatinib.

The other ingredients are:
- Capsule content: colloidal anhydrous silica, microcrystalline cellulose
- Capsule shell 40 mg: gelatin, titanium dioxide (E171), and iron oxide (E172).
- Capsule shell 80 mg: gelatin, titanium dioxide (E171), and brilliant blue FCF (E133).
- Black ink: Shellac, Ethanol (96 per cent), Isopropyl alcohol, Butanol, Propylene glycol, Water, purified, Ammonia solution (concentrated), Potassium hydroxide, Iron oxide black

What Retsevmo looks like and contents of the pack
Retsevmo 40 mg is supplied as grey opaque hard gelatin capsule, with black "Lilly", "3977" and "40 mg" script.

Retsevmo 80 mg is supplied as blue opaque hard gelatin capsule, with black "Lilly", "2980" and "80 mg" script.

Retsevmo is available in a white opaque bottle with a plastic screw cap, containing 60 hard capsules of 40 mg and either 60 or 120 hard capsules of 80 mg. Each carton contains one bottle.

Retsevmo is available in blister packs of 14, 42, 56 or 168 hard capsules of 40 mg and 14, 28, 56 or 112 hard capsules of 80 mg.

Not all the pack sizes may be marketed.

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

Manufacturer
Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Package leaflet: Information for the patient

Retsevmo 40 mg film-coated tablets
Retsevmo 80 mg film-coated tablets
Retsevmo 120 mg film-coated tablets
Retsevmo 160 mg film-coated tablets
selpercatinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- This leaflet has been written as though the person taking the medicine is reading it. If you are giving this medicine to your child, please replace "you" with "your child" throughout.

What is in this leaflet

1. What Retsevmo is and what it is used for
2. What you need to know before you take Retsevmo
3. How to take Retsevmo
4. Possible side effects
5. How to store Retsevmo
6. Contents of the pack and other information

1. What Retsevmo is and what it is used for

Retsevmo is an anticancer medicine containing the active substance selpercatinib.

It is used to treat the following cancers which are caused by certain abnormal changes in the RET gene and which have spread and/or cannot be removed by surgery:
- A type of lung cancer called non-small cell lung cancer, in adults who have not previously been treated with a *RET* inhibitor medicine.
- Thyroid cancer (any type) in adults and adolescents 12 years and older if radioactive iodine treatment, when appropriate, has failed to control your cancer.
- A rare type of thyroid cancer called medullary thyroid cancer in adults and adolescents 12 years and older.
- Solid tumours (cancer) in other parts of the body in adults after prior therapies have failed to control the cancer.

Your doctor will perform a test to check if your cancer has a change in the RET gene to make sure that Retsevmo is right for you.

How Retsevmo works
In patients whose cancer has an altered RET gene, the change in the gene causes the body to make an abnormal RET protein, which can lead to uncontrolled cell growth and cancer. Retsevmo blocks the action of the abnormal RET protein and so may slow or stop the growth of the cancer. It may also help to shrink the cancer.

If you have any questions about how Retsevmo works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take Retsevmo

Do not take Retsevmo
- if you are allergic to selpercatinib or any of the other ingredients of this medicine (listed in section 6).
- if you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking Retsevmo.

Warnings and precautions
Talk to your doctor before taking Retsevmo:
- If you have lung or breathing problems other than lung cancer.
- If you have high blood pressure.
- If you have been told that you have an abnormality of your heart tracing after an electrocardiogram (ECG) known as prolonged QT interval.
- If you have problems with your thyroid or levels of thyroid hormone.
- Retsevmo may affect fertility in females and males, which may affect your ability to have children. Talk to your doctor if this is a concern for you.
- If you have a recent history of significant bleeding.

Retsevmo may cause hypersensitivity reactions such as fever, rash and pain. If you experience any of these reactions, talk to your doctor. After checking your symptoms, your doctor may ask you to take corticosteroids until your symptoms are better.

A fast breakdown of cancer cells (tumour lysis syndrome, TLS) can occur when you are taking Retsevmo. This can cause irregular heartbeat, kidney failure or abnormal blood test results. Talk to your doctor if you have a history of kidney problems or low blood pressure, because this may increase the risks associated with TLS.

Retsevmo may cause irregular hip joint growth or damage in paediatric patients (<18 years of age). If you experience pain in the hip or knee or have an unexplained limp, talk to your doctor.

This medicine can cause serious skin reactions. Stop using Retsevmo and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

See section 4, “Possible side effects”, and talk to your doctor if you have any symptoms.

What your doctor will check before and during your treatment
- Retsevmo may cause severe, life-threatening, or fatal inflammation of the lungs. Your doctor will monitor you before and during treatment with Retsevmo for symptoms. Tell your doctor right away if you notice any symptoms of lung problems including breathlessness, cough and raised temperature.
- Retsevmo may affect your blood pressure. You will have your blood pressure measured before and during treatment with Retsevmo.
- Retsevmo may affect the way your liver works. Tell your doctor right away if you develop symptoms of liver problems including: jaundice (yellow discoloration of the skin and eyes), loss of appetite, nausea or vomiting, or pain on the upper right side of your stomach area.
- Retsevmo may result in abnormal ECGs. You will have an ECG taken before and during your treatment with Retsevmo. Tell your doctor if you experience fainting as it may be a symptom of abnormal ECG.
- Retsevmo may affect how your thyroid works. Your doctor will monitor your thyroid function before and during treatment with Retsevmo.

- You will have regular blood tests before and during treatment with Retsevmo, to check your liver function and electrolytes (such as sodium, potassium, magnesium and calcium) in your blood.
- If you are under 18 years of age, your doctor may monitor your growth during treatment. If you have hip, knee, or other leg pain let your doctor know.

Children and adolescents
Retsevmo is not intended for use in patients less than 18 years of age in lung cancer.
The thyroid cancer (including medullary thyroid cancer) indications do not cover children younger than 12 years of age.

Other medicines and Retsevmo
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or pharmacist before taking Retsevmo if you are taking the following:
- medicines that may increase the concentration of Retsevmo in the blood:
    - Clarithromycin (used to treat bacterial infections)
    - Itraconazole, ketoconazole, posaconazole, voriconazole (used to treat fungal infections)
    - Atazanavir, ritonavir, cobicistat (used to treat HIV infections/AIDS)
- medicines that may reduce the effectiveness of Retsevmo:
    - Carbamazepine (used to treat epilepsy, nerve pain, bipolar disorder)
    - Rifampicin (used to treat tuberculosis (TB) and some other infections)
    - St. John's wort (a herbal product used to treat mild depression and anxiety)
    - Omeprazole, lansoprazole, or other proton pump inhibitors used to treat heartburn, ulcers, and acid reflux. If you are taking any of these medicines, then take Retsevmo with a full meal
    - Ranitidine, famotidine or other H2 blockers used to treat ulcers and acid reflux. If you are taking any of these medicines, then you need to take them 2 hours after taking Retsevmo
- medicines whose concentration in the blood might be increased by Retsevmo:
    - Repaglinide (used to treat type 2 diabetes and control blood sugar)
    - Dasabuvir (used to treat hepatitis C)
    - Selexipag (used to treat pulmonary arterial hypertension)
    - Digoxin (used to treat heart disorders)
    - Lovastatin and simvastatin (used to treat high cholesterol)
    - Dabigatran (used to prevent and treat blood clots)
- medicines that may be less effective when taken with Retsevmo:
    - Levothyroxine (used to treat hypothyroidism)

Pregnancy, breast-feeding and fertility
Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor before taking this medicine.

You should not use Retsevmo during pregnancy, since the effect of Retsevmo on the unborn is not known.

Breast-feeding
Do not breast-feed during treatment with Retsevmo as Retsevmo could harm a breast-fed baby. It is not known if Retsevmo passes into breast milk. You should not breast-feed for at least one week after your last dose of Retsevmo.

Contraception
It is recommended that women avoid becoming pregnant and that men do not father children during treatment with Retsevmo, because this medicine could harm the baby. If there is any possibility that

the person taking this medicine may become pregnant or father a child, they must use adequate contraception during treatment and for at least one week after the last dose of Retsevmo.

Fertility
Retsevmo can affect your ability to have children. Talk to your doctor to seek advice about fertility preservation prior to treatment.

Driving and using machines
You should take special care when driving and using machines as you may feel tired or dizzy while taking Retsevmo.

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

3. How to take Retsevmo

Always take this medicine exactly as your doctor or pharmacist has told you, at the dose prescribed for you. Check with your doctor or pharmacist if you are not sure.

How much to take
Your doctor will prescribe the right dose for you. The maximum recommended dose is as follows:

- Less than 50 kg body weight: 120 mg twice daily.

- 50 kg body weight or greater: 160 mg twice daily.

Retsevmo is taken twice a day at about the same time every day, preferably in the morning and evening.
If you get certain side effects while you are taking Retsevmo your doctor may lower your dose or stop treatment temporarily or permanently.

You can take the tablets either with or without food. Swallow the tablet whole with a glass of water. Do not chew, crush or split the tablet before swallowing to ensure you receive the correct dose.

In case you have difficulty swallowing larger tablets whole, talk to your doctor about taking multiple smaller tablets instead to achieve your prescribed dose.

If you take more Retsevmo than you should
If you take too many tablets, or if someone else takes your medicine, contact a doctor or hospital for advice. Medical treatment may be necessary.

If you forget to take Retsevmo
If you vomit after taking the dose or forget a dose, take your next dose at your usual time. Do not take a double dose to make up for the forgotten or vomited dose.

If you stop taking Retsevmo
Do not stop taking Retsevmo unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side-effects, although not everybody gets them.

Stop using Retsevmo and seek medical attention immediately if you notice any of the following symptoms of serious skin reactions:
- Reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms [Stevens-Johnson syndrome (SJS)].

Contact your doctor immediately for any of the following:
- Lung or breathing problems other than lung cancer with symptoms such as breathlessness, cough and raised temperature (which may affect more than 1 in 10 people)
- Liver problems (which may affect more than 1 in 10 people and can be associated with abnormalities in liver blood tests, such as increased liver enzymes) including: yellow discoloration of the skin and eyes (jaundice), darkening of the urine, loss of appetite, nausea or vomiting, or pain on the upper right side of your stomach area
- Allergic reaction typically shown by fever and muscle and joint pain followed by rash (which may affect up to 1 in 10 people)
- High blood pressure (which may affect more than 1 in 10 people)
- Bleeding with symptoms such as coughing up blood

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)
- Low blood levels of calcium
- Reduced number of white blood cells (e.g., lymphocytes, neutrophils, etc.)
- Low blood levels of albumin
- Fluid retention that may cause swelling in your hands or ankles (oedema)
- Diarrhoea
- Increased blood levels of creatinine in tests, which may indicate that kidneys are not working properly (renal disorders)
- Fatigue or tiredness
- Dry mouth
- Low blood levels of sodium
- Reduced number of blood platelets, which may cause bleeding and/or bruising
- Rash
- Pain in the belly
- Constipation
- Low levels of haemoglobin, which may cause anaemia
- Low blood levels of magnesium
- Nausea (feeling sick)
- Headache
- Vomiting
- Bleeding symptoms
- Impotence
- Decreased appetite
- Abnormal ECG
- Low blood levels of potassium
- Dizziness
- Infection of the urinary tract
- Fever or high temperature
- Inflammation of the mucous membrane of the mouth
- Reduced thyroid activity

Common (may affect more than 1 in 100 people)
- Lymph fluid may build up in the lining of your lungs or your stomach cavity, which may cause breathing problems or enlargement of the stomach
- Irregular hip joint growth or damage causing pain or limp in patients < 18 years of age

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Retsevmo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the inner seal is broken or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Retsevmo contains
The active substance is selpercatinib. Each film-coated tablet contains 40, 80, 120 or 160 mg selpercatinib.

The other ingredients are:
- Tablet content: microcrystalline cellulose, mannitol, croscarmellose sodium, hydroxypropylcellulose, sodium stearyl fumarate
- Film-coating: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, red iron oxide (E172) [80 mg, 120 mg and 160 mg tablets only], and black iron oxide (E172) [40 mg, 80 mg and 120 mg tablets only].

What Retsevmo looks like and contents of the pack
Retsevmo 40 mg is supplied as a light grey, round film-coated tablet debossed on one side with "5340" and debossed with "Ret 40" on the other.

Retsevmo 80 mg is supplied as a dark red-purple, round film-coated tablet debossed on one side with "6082" and debossed with "Ret 80" on the other.

Retsevmo 120 mg is supplied as a light purple, round film-coated tablet debossed on one side with "6120" and debossed with "Ret 120" on the other.

Retsevmo 160 mg is supplied as a light pink, round film-coated tablet debossed on one side with "5562" and debossed with "Ret 160" on the other.

Retsevmo is available in blister packs of 30, 56 or 60 film-coated tablets of 40 mg, 80 mg, 120 mg and 160 mg.

Not all the pack sizes may be marketed.

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

Manufacturer
Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for selpercatinib, the scientific conclusions of PRAC are as follows:

In view of available data on Stevens-Johnson syndrome (SJS) from the literature, including a close temporal relationship in 1 case from literature, and a diagnosis based on clinical picture together with histopathological findings, the PRAC Rapporteur considers a causal relationship between selpercatinib and Stevens-Johnson syndrome is at least a reasonable possibility. The PRAC Rapporteur concluded that the product information of products containing selpercatinib should be amended accordingly

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for selpercatinib the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing selpercatinib is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.

Selpercatinib: Core Data Sheet

2頁目から最終頁までは非公表のため削除

レットヴィモカプセル 40mg
レットヴィモカプセル 80mg
レットヴィモ錠 40mg
レットヴィモ錠 80mg

1.7　同種同効品一覧表

日本イーライリリー株式会社

目次

1.7　同種同効品一覧表 1

1.7　同種同効品一覧表

セルペルカチニブは、選択的な RET（Rearranged during Transfection）受容体型チロシンキナーゼ阻害剤である。本剤は、「*RET* 融合遺伝子陽性の進行・再発の固形腫瘍」、及び「*RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌」の効能又は効果を有している。

RET 融合遺伝子陽性の固形腫瘍、及び *RET* 遺伝子変異陽性の甲状腺髄様癌に対して特異的な分子標的薬はない。

したがって、現時点で同種同効薬は存在しない。

レットヴィモカプセル 40mg
レットヴィモカプセル 80mg
レットヴィモ錠 40mg
レットヴィモ錠 80mg

1.8　添付文書（案）

日本イーライリリー株式会社

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1.8 添付文書（案）

1.8.1 添付文書（案）

レットヴィモカプセル 40mg、レットヴィモカプセル 80mg 及びレットヴィモ錠 40mg、レットヴィモ錠 80mg の電子化された添付文書（案）を以下に示す。

最新の添付文書を参照すること

*20xx 年 x 月改訂（第 x 版、用法及び用量変更）
2026 年 2 月改訂（第 9 版）

日本標準商品分類番号
874291

抗悪性腫瘍剤　RET 注2) 受容体型チロシンキナーゼ阻害剤

貯　　法：室温保存
有効期間：36 ヵ月

セルペルカチニブカプセル

レットヴィモ® カプセル40mg
レットヴィモ® カプセル80mg
Retevmo® Capsules

劇薬
処方箋医薬品注1)
注 1）注意－医師等の処方箋により使用すること
注 2）RET ： rearranged during transfection

	40mg	80mg
承認番号	30300AMX00448	30300AMX00449
販売開始	2021 年 12 月	2021 年 12 月

1. 警告
本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）
本剤の成分に対しアナフィラキシー等の重篤な過敏症の既往歴のある患者

3. 組成・性状
3.1 組成

販売名	レットヴィモカプセル 40mg	レットヴィモカプセル 80mg
有効成分	1 カプセル中 セルペルカチニブ 40mg	1 カプセル中 セルペルカチニブ 80mg
添加剤	内容物：軽質無水ケイ酸、結晶セルロース カプセル本体：ゼラチン、酸化チタン、黒酸化鉄（40mg のみ含有）、青色 1 号（80mg のみ含有）	

3.2 製剤の性状

販売名	レットヴィモカプセル 40mg	レットヴィモカプセル 80mg
性状・剤形	灰色不透明の硬カプセル剤	青色不透明の硬カプセル剤
外形	 2 号カプセル	 0 号カプセル
寸法・重量	長径：約 18.0mm 短径：約 6.4mm 重量：約 194mg	長径：約 21.7mm 短径：約 7.6mm 重量：約 363mg
識別コード	Lilly 3977	Lilly 2980

4. 効能又は効果
○*RET* 融合遺伝子陽性の進行・再発の固形腫瘍
○*RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌

5. 効能又は効果に関連する注意
〈*RET* 融合遺伝子陽性の進行・再発の非小細胞肺癌〉
5.1　十分な経験を有する病理医又は検査施設における検査により、*RET* 融合遺伝子陽性が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器注) を用いること。
*5.2　「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。［17.1.1、17.1.2 参照］
5.3　本剤の術後補助療法における有効性及び安全性は確立していない。
〈*RET* 融合遺伝子陽性の進行・再発の甲状腺癌〉
5.4　十分な経験を有する病理医又は検査施設における検査により、*RET* 融合遺伝子陽性が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器注) を用いること。
5.5　放射性ヨウ素による治療の適応となる患者においては、当該治療を優先すること。
〈*RET* 融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）〉
5.6　十分な経験を有する病理医又は検査施設における検査により、*RET* 融合遺伝子陽性が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器注) を用いること。
5.7　組織球症患者は本剤の投与対象となり得る。
*5.8　臨床試験に組み入れられた患者のがん種等について、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。［17.1.1、17.1.2 参照］
5.9　本剤の手術の補助療法における有効性及び安全性は確立していない。
〈*RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌〉
5.10　十分な経験を有する病理医又は検査施設における検査により、*RET* 遺伝子変異が確認された患者に投与すること。生殖細胞系列の *RET* 遺伝子変異が陰性又は不明の場合は、承認された体外診断用医薬品又は医療機器注) を用いて検査を行うこと。
*5.11　「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。［17.1.1、17.1.2 参照］

注）承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

*6. 用法及び用量
通常、成人にはセルペルカチニブとして 1 回 160mg を 1 日 2 回経口投与する。なお、患者の状態により適宜減量する。
通常、2 歳以上の小児には体表面積に合わせて次の投与量（セルペルカチニブとして 1 日量約 184mg/m²）を経口投与する。なお、患者の状態により適宜減量する。

小児の用量

体表面積	投与量
0.33m² 以上 0.66m² 未満	1 回 40mg　1 日 3 回
0.66m² 以上 1.2m² 未満	1 回 80mg　1 日 2 回
1.2m² 以上 1.6m² 未満	1 回 120mg　1 日 2 回
1.6m² 以上	1 回 160mg　1 日 2 回

7. 用法及び用量に関連する注意

7.1 他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。

*7.2 本剤投与により副作用が発現した場合には、以下の基準を考慮して、休薬・減量・中止すること。

成人の場合　本剤の減量の目安

減量レベル	投与量
通常投与量	1回160mg　1日2回
1段階減量	1回120mg　1日2回
2段階減量	1回80mg　1日2回
3段階減量	1回40mg　1日2回

小児の場合　本剤の減量の目安

体表面積	減量レベル	投与量
0.33m²以上 0.66m²未満	通常投与量	1回40mg　1日3回
	1段階減量	1回40mg　1日2回
	2段階減量	1回40mg　1日1回
	3段階減量	投与中止
0.66m²以上 1.2m²未満	通常投与量	1回80mg　1日2回
	1段階減量	1回40mg　1日2回
	2段階減量	1回40mg　1日1回
	3段階減量	投与中止
1.2m²以上 1.6m²未満	通常投与量	1回120mg　1日2回
	1段階減量	1回80mg　1日2回
	2段階減量	1回40mg　1日1回 及び1回80mg　1日1回 (1日量120mg)
	3段階減量[注1)]	1回40mg　1日1回
1.6m²以上	通常投与量	1回160mg　1日2回
	1段階減量	1回120mg　1日2回
	2段階減量	1回80mg　1日2回
	3段階減量	1回40mg　1日2回

注1）過敏症発現時のみ（過敏症以外で2段階減量において忍容性が得られない場合、投与中止）

副作用に対する休薬、減量及び中止基準

副作用	程度[注2)]	処置
ALT又はAST増加	グレード3又は4	グレード1以下に回復するまで休薬し、回復後は2段階減量して投与再開できる。 再開後に2週間以上再発しない場合には、1段階増量することができる。更に4週間以上再発しない場合には、もう1段階増量することができる。 減量した用量で投与中に再発した場合には、中止する。
QT間隔延長	QTc間隔>500msec	QTc間隔<470msecに回復するまで休薬し、回復後は1段階減量して投与再開できる。 2段階減量した用量で投与中に再発した場合には、中止する。
	重篤な不整脈を疑う所見や症状が認められた場合	中止する。
高血圧	グレード3又は4	回復するまで休薬し、回復後は1段階減量して投与再開できる。
過敏症(アナフィラキシー等の重篤な過敏症を除く) [11.1.3参照]	グレード1～4	回復するまで休薬し、副腎皮質ステロイドの全身投与を考慮する。回復後は副腎皮質ステロイドを併用しながら3段階減量[注3)]して投与再開できる。 再開後に7日以上再発しない場合には、1段階ずつ発現時の用量まで増量できる。増量後に7日以上再発しない場合には、副腎皮質ステロイドを漸減する。
間質性肺疾患	グレード2	回復するまで休薬し、回復後は1段階減量して投与再開できる。
	グレード3又は4	中止する。
上記以外の副作用	グレード3又は4	回復するまで休薬し、回復後は1段階減量して投与再開できる。

注2）グレードはNCI-CTCAE ver. 4.03に準じる。
注3）体表面積1.2m²以上の場合のみ

8. 重要な基本的注意

8.1 肝機能障害があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に肝機能検査を行い、患者の状態を十分に観察すること。[11.1.1参照]

*8.2 QT間隔延長があらわれることがあるので、本剤の投与開始前には患者のQTc間隔が成人470msec、12歳未満の小児440msec以下であることを確認するとともに血清電解質検査（カリウム、マグネシウム等）を行うこと。心電図及び血清電解質検査を投与開始後1週間時点及び投与開始後6ヵ月間は毎月1回行い、以降も必要に応じて行うこと。また、必要に応じて電解質補正を行うこと。[11.1.2、17.3.1参照]

8.3 高血圧があらわれることがあるので、本剤の投与開始前に血圧が適切に管理されていることを確認すること。本剤投与中は定期的に血圧を測定すること。

8.4 間質性肺疾患があらわれることがあるので、本剤の投与にあたっては、初期症状（呼吸困難、咳嗽、発熱等）の確認及び胸部画像検査の実施等、患者の状態を十分に観察すること。また、患者に副作用について説明するとともに、間質性肺疾患の初期症状が発現した場合には、速やかに医療機関を受診するよう説明すること。[9.1.3、11.1.5参照]

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 QT間隔延長のおそれ又はその既往歴のある患者

QT間隔延長が発現するおそれがある。先天性/後天性QT延長症候群又はその他不整脈の要因になる病態を有する患者には慎重に投与すること。[11.1.2、17.3.1参照]

9.1.2 高血圧症の患者

高血圧が悪化するおそれがある。[11.1.4参照]

9.1.3 間質性肺疾患のある患者又はその既往歴のある患者

間質性肺疾患が発現又は増悪するおそれがある。[8.4、11.1.5参照]

9.3 肝機能障害患者

9.3.1 重度の肝機能障害のある患者（Child-Pugh分類C）

減量を考慮するとともに、患者の状態をより慎重に観察し、副作用の発現に十分注意すること。本剤の血中濃度が上昇し、副作用が増強されるおそれがある。[16.6.2参照]

9.4 生殖能を有する者

9.4.1 妊娠する可能性のある女性には、本剤投与中及び最終投与後1ヵ月間において避妊する必要性及び適切な避妊法について説明すること。[9.5参照]

9.4.2 男性には、本剤投与中及び最終投与後1週間においてバリア法（コンドーム）を用いて避妊する必要性について説明すること。[15.2.1参照]

9.4.3 成長期にある若年男性又は男児に投与する場合には、造精機能の低下があらわれる可能性があることを考慮すること。幼若ラットにおいて、精巣の精上皮変性、精巣上体の精子枯渇、精子運動率低値、異常形態精子比率高値及び受胎能の低下が認められ、精巣及び精巣上体の所見に回復性は認められていない[1)]。

9.5 妊婦

妊婦又は妊娠している可能性のある女性には治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。ラットを用いた胚・胎児発生毒性試験において、臨床曝露量（AUC）と同程度の曝露量で胎児死亡及び奇形が認められている[1)]。[9.4.1参照]

9.6 授乳婦

授乳しないことが望ましい。乳汁移行に関するデータはないが、本剤はBCRPの基質であるため、乳汁移行の可能性がある。

9.7 小児等

9.7.1 成長期にある若年者においては、骨成長について以下の点に注意すること。

・骨端線に異常がないか十分に観察すること。骨端線に異常が認められた場合には、投与継続の可否を慎重に判断すること。
・関節痛及び歩行障害について十分に観察すること。大腿骨頭すべり症等の骨端離開があらわれることがある。
［15.2.2 参照］

9.7.2 2歳未満の小児等を対象とした臨床試験は実施していない。

*10. 相互作用

本剤は、主にCYP3A4によって代謝され、CYP2C8、CYP3A、P-gp及びBCRPの阻害作用を示す。また、本剤の溶解度はpHの上昇により低下する。

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
CYP2C8の基質となる薬剤 レパグリニド ピオグリタゾン モンテルカスト等 ［16.7.6参照］	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤がCYP2C8を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。
CYP3Aの基質となる薬剤 ミダゾラム トリアゾラム ロミタピド等 ［16.7.5参照］	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤がCYP3Aを阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。
CYP3A阻害剤 イトラコナゾール クラリスロマイシン エリスロマイシン等 ［16.7.1、16.7.2参照］	本剤の副作用が増強されるおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤の減量を考慮するとともに、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	これらの薬剤がCYP3Aを阻害することにより、本剤の血中濃度が上昇する可能性がある。
CYP3A誘導剤 リファンピシン フェニトイン ボセンタン等 ［16.7.3、16.7.4参照］	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避け、CYP3A誘導作用のない薬剤への代替を考慮すること。	これらの薬剤等がCYP3Aを誘導することにより、本剤の血中濃度が低下する可能性がある。
セイヨウオトギリソウ(St. John's Wort、セント・ジョーンズ・ワート)含有製品	本剤の有効性が減弱するおそれがあるので、摂取しないよう注意すること。	
プロトンポンプ阻害剤 オメプラゾール ランソプラゾール エソメプラゾール等 ［16.7.7参照］	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤とともに食後に投与すること。	これらの薬剤による胃内pHの上昇により、本剤の吸収が低下し、本剤の血中濃度が低下する可能性がある。
H_2受容体拮抗剤 ラニチジン ファモチジン シメチジン等 ［16.7.8参照］	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤と服用時間をずらすこと(ラニチジンを本剤投与10時間前及び2時間後に投与したときの本剤の血中濃度への影響は限定的であった)。	
制酸剤 炭酸カルシウム 水酸化マグネシウム 水酸化アルミニウム等	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤と服用時間をずらすこと(制酸剤を本剤投与2時間前又は2時間後に投与したときの本剤の血中濃度への影響は限定的であった)。	
治療域の狭いP-gpの基質となる薬剤 ジゴキシン シロリムス エベロリムス等 ［16.7.9参照］	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤がP-gpを阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。
BCRPの基質となる薬剤 ロスバスタチン メトトレキサート イマチニブ等 ［16.7.10参照］		本剤がBCRPを阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

***11.1.1 肝機能障害**（37.8%）
［8.1参照］

11.1.2 QT間隔延長（13.9%）
［8.2、9.1.1、17.3.1参照］

***11.1.3 過敏症**（4.9%）
発疹、発熱等の症状を伴う遅発性の過敏症があらわれることがある。［7.2参照］

***11.1.4 高血圧**（28.0%）
［9.1.2参照］

***11.1.5 間質性肺疾患**（0.6%）
［8.4、9.1.3参照］

11.2 その他の副作用

副作用分類	20%以上	5～20%未満	5%未満	頻度不明
*消化器	口内乾燥(31.9%)、下痢	便秘、悪心、口内炎、腹痛	嘔吐	
*一般・全身及び投与部位反応	疲労	浮腫	発熱	
呼吸器			鼻出血、肺炎	
感染症			尿路感染	
内分泌			甲状腺機能低下症	
代謝・栄養障害		食欲減退		
精神神経系		頭痛	浮動性めまい	
皮膚		発疹		
生殖器		勃起不全		
血液		血小板減少、白血球減少、好中球減少	リンパ球減少、貧血	
*臨床検査値異常		血中クレアチニン増加	低マグネシウム血症、低アルブミン血症、低カリウム血症、低カルシウム血症	
*その他			乳び腹水	乳び胸

14. 適用上の注意

14.1 薬剤交付時の注意

PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。PTPシートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。

15. その他の注意

15.2 非臨床試験に基づく情報

15.2.1 セルペルカチニブは、ラット小核試験において、臨床用量160mg1日2回で得られるC_{max}の5.2倍に相当する用量で遺伝毒性が陽性であった[1)]。［9.4.2参照］

15.2.2 動物試験（成長板が閉鎖していない幼若ラット、若齢ラット及び若齢ミニブタ）において、本剤の反復投与により骨端成長板の異常(骨端軟骨の肥大、過形成及び異形成)が、ヒトに160mg1日2回の用量で投与したときの臨床曝露量よりも低い曝露量で

認められている。また、幼若ラットにおいて、骨端成長板の変化に関連して、骨密度及び大腿骨長の低値が、ヒトに 160mg1 日 2 回の用量で投与したときの臨床曝露量のそれぞれ 0.8 倍及び 1.9 倍で認められている[1]。[9.7.1 参照]

15.2.3 ラットを用いた 2 年間がん原性試験において、ヒトに 160mg1 日 2 回の用量で投与したときの臨床曝露量に相当する用量で雌に膣腫瘍が認められている[2]。

16. 薬物動態

16.1 血中濃度

16.1.1 単回及び反復投与

進行固形腫瘍患者 94 例にセルペルカチニブカプセル 160mg を単回経口投与したときの血漿中濃度推移及び薬物動態パラメータは以下のとおりであった[3]（外国人データ）。

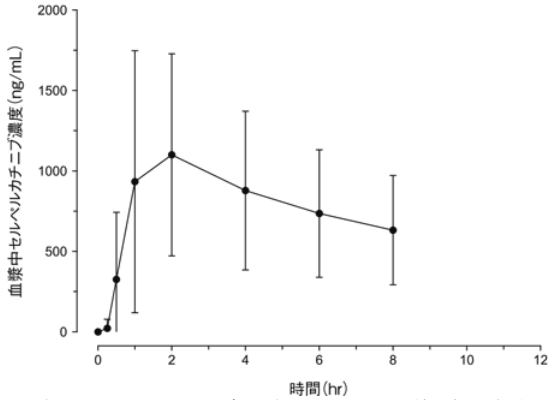


図 1）セルペルカチニブカプセル 160mg を単回経口投与後（第 1 サイクル第 1 日目）の血漿中濃度推移（平均値±標準偏差）

表 1）セルペルカチニブカプセル 160mg を単回経口投与後（第 1 サイクル第 1 日目）の薬物動態パラメータ（幾何平均値及び変動係数%）

例数	94
C_{max} (ng/mL)	1120 (85.7)
t_{max} 注 1) (hr)	1.96 (0.50-7.83)
AUC_{τ} (ng・hr/mL)	7430 注 2) (67.5)

注 1）中央値（最小値-最大値）
注 2）例数=71
τ：投与間隔（12 時間）

日本人の進行固形腫瘍患者 58 例にセルペルカチニブカプセル 160mg を 1 日 2 回反復経口投与したときの定常状態における血漿中濃度推移及び薬物動態パラメータは以下のとおりであった[3]。

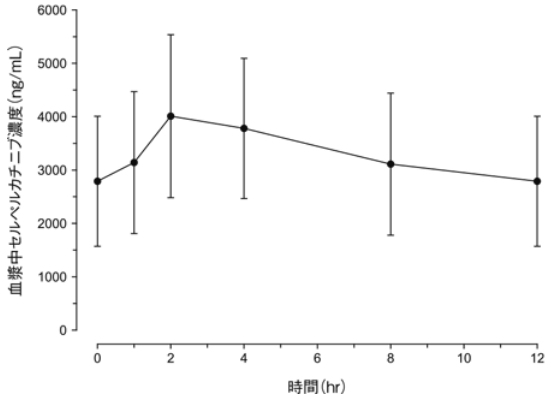


図 2）セルペルカチニブカプセル 160mg を 1 日 2 回反復経口投与後（第 1 サイクル第 8 日目）の定常状態における血漿中濃度推移（平均値±標準偏差）

表 2）セルペルカチニブカプセル 160mg を 1 日 2 回反復経口投与後（第 1 サイクル第 8 日目）の定常状態における薬物動態パラメータ（幾何平均値及び変動係数%）

例数	58
$C_{max,ss}$ (ng/mL)	4060 (34.4)
$t_{max,ss}$ 注 3) (hr)	2.08 (0.00-8.10)
$AUC_{\tau,ss}$ (ng・hr/mL)	37100 (39.3)
CL_{ss}/F (L/hr)	4.31 (39.3)

注 3）中央値（最小値-最大値）
τ：投与間隔（12 時間）

血漿中濃度は反復投与後 8 日までに定常状態に到達した。また、セルペルカチニブカプセル 160mg を 1 日 2 回反復経口投与した際の投与 8 日目におけるセルペルカチニブの蓄積率は 3.40 であった。

16.2 吸収

16.2.1 絶対的バイオアベイラビリティ

健康成人 6 例にセルペルカチニブカプセル 160mg を単回経口投与したときの絶対的バイオアベイラビリティの幾何平均値は 73.2%であった[4]（外国人データ）。

16.2.2 食事の影響

健康成人 20 例にセルペルカチニブカプセル 160mg を高脂肪食摂取後に単回経口投与したとき、空腹時投与に対する食後投与におけるセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比はそれぞれ 0.862 及び 1.09 であった[5]（外国人データ）。

16.3 分布

16.3.1 蛋白結合率

セルペルカチニブのヒト血漿タンパク結合率は約 96%であり、濃度依存性は認められなかった（*in vitro*）[6]。

16.3.2 血液/血漿中濃度比

セルペルカチニブの血液/血漿中濃度比は約 0.7 であった（*in vitro*）[7]。

16.4 代謝

セルペルカチニブは主として CYP3A4 により代謝される（*in vitro*）[8]。健康成人 6 例に［^{14}C］-セルペルカチニブ 160mg を単回経口投与したとき、投与 168 時間後までの血漿中には主に未変化体が検出された（血漿中総放射能に対する割合は、86.2%）[4]（外国人データ）。

16.5 排泄

健康成人 6 例に［^{14}C］-セルペルカチニブ 160mg を単回経口投与したとき、投与 432 時間後までに投与した放射能の約 69%（未変化体は約 14%）が糞便中に排泄され、約 24%（未変化体は約 11.5%）が尿中に排泄された[4]（外国人データ）。

16.6 特定の背景を有する患者

16.6.1 腎機能障害患者

セルペルカチニブカプセル 160mg を単回経口投与したとき、腎機能正常被験者（10 例）に対する軽度の腎機能障害患者（8 例）の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.30 及び 1.07 であった。腎機能正常被験者（10 例）に対する中等度の腎機能障害患者（8 例）の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.67 及び 1.89 であった。腎機能正常被験者（10 例）に対する重度の腎機能障害患者（7 例）の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.04 及び 1.54 であった[9]（外国人データ）。血液透析の有無によらず、末期腎不全患者に関するデータはない。

16.6.2 肝機能障害患者

セルペルカチニブカプセル 160mg を単回経口投与したとき、肝機能正常被験者（12 例）に対する軽度の肝機能障害患者（8 例）の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.78 及び 1.33 であった。肝機能正常被験者（12 例）に対する中等度の肝機能障害患者（8 例）の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 0.989 及び 0.991 であった。肝機能正常被験者（12 例）に対する重度の肝機能障害患者（8 例）の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 2.32 及び 3.28 であった[10]（外国人データ）。[9.3.1 参照]

*16.6.3 小児

国際共同第 I/II 相試験（LIBRETTO-001 試験及び LIBRETTO-121 試験）に組み入れられた 839 例（18 歳未満の患者 34 例を含む）のデータを用いて母集団薬物動態モデルを構築した。年齢によりセルペルカチニブの薬物動態に臨床的に意味のある差は認められなかったが、体重の増加に伴いセルペルカチニブの V_{ss}/F 及び CL/F は増加した。母集団薬物動態モデルを用いて、仮想患者の体表面積及び体重情報に基づく薬物動態シミュレーションを実施した結果、①体表面積 0.33m² 以上 0.66m² 未満の患者に 40mg1 日 3 回、②体表面積 0.66m² 以上 1.2m² 未満の患者に 80mg1 日 2 回、③体表面積 1.2m² 以上 1.6m² 未満の患者に 120mg1 日 2 回、④体表面積 1.6m² 以上の患者に 160mg1 日 2 回をそれぞれ反復経口投与した際の、定常状態におけるセルペルカチニブの C_{max}（ng/mL）及び AUC_{24h}（ng・hr/mL）の中央値は、①3120 及び 57700、②3360 及び 58300、③3190 及び 58600 並びに④3550 及び 66400 と推定された[11]。

16.7 薬物相互作用

16.7.1 イトラコナゾール

健康成人 12 例にイトラコナゾール（強い CYP3A 阻害剤）200mg を 1 日 1 回反復経口投与し、セルペルカチニブカプセル 160mg を単回経口投与したとき、セルペルカチニブカプセル単独投与時に対するイトラコナゾール併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、1.30 及び 2.33 であった[12]（外国人データ）。［10.2 参照］

16.7.2 フルコナゾール、ジルチアゼム

生理学的薬物動態モデルに基づいたシミュレーションにおいて、セルペルカチニブカプセル（160mg を単回経口投与）単独投与時に対するフルコナゾール（中程度の CYP3A 阻害剤）（200mg を 1 日 1 回反復経口投与）併用投与時のセルペルカチニブの C_{max} 及び AUC の幾何平均値の比は、それぞれ 1.20 及び 2.48 と推定された。セルペルカチニブカプセル（160mg を単回経口投与）単独投与時に対するジルチアゼム（中程度の CYP3A 阻害剤）（60mg を 1 日 3 回反復経口投与）併用投与時のセルペルカチニブの C_{max} 及び AUC の幾何平均値の比は、それぞれ 1.17 及び 2.18 と推定された[13]。［10.2 参照］

16.7.3 リファンピシン

健康成人 12 例にリファンピシン（強い CYP3A 誘導剤）600mg を 1 日 1 回反復経口投与し、セルペルカチニブカプセル 160mg を単回経口投与したとき、セルペルカチニブカプセル単独投与時に対するリファンピシン併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.301 及び 0.133 であった[12]（外国人データ）。［10.2 参照］

16.7.4 ボセンタン、モダフィニル

生理学的薬物動態モデルに基づいたシミュレーションにおいて、セルペルカチニブカプセル（160mg を単回経口投与）単独投与時に対するボセンタン（中程度の CYP3A 誘導剤）（125mg を 1 日 2 回反復経口投与）併用投与時のセルペルカチニブの C_{max} 及び AUC の幾何平均値の比は、それぞれ 0.71 及び 0.53 と推定された。セルペルカチニブカプセル（160mg を単回経口投与）単独投与時に対するモダフィニル（中程度の CYP3A 誘導剤）（200mg を 1 日 1 回 7 日間経口投与後に 400mg を 1 日 1 回反復経口投与）併用投与時のセルペルカチニブの C_{max} 及び AUC の幾何平均値の比は、それぞれ 0.86 及び 0.64 と推定された[13]。［10.2 参照］

16.7.5 ミダゾラム

健康成人 16 例にセルペルカチニブカプセル 160mg を 1 日 2 回反復経口投与し、ミダゾラム（CYP3A の基質）2mg を単回経口投与したとき、ミダゾラム単独投与時に対するセルペルカチニブカプセル併用投与時のミダゾラムの C_{max} 及び AUC_{inf} の幾何平均値の比は、1.39 及び 1.54 であった[14]（外国人データ）。［10.2 参照］

16.7.6 レパグリニド

健康成人 16 例にセルペルカチニブカプセル 160mg を 1 日 2 回反復経口投与し、レパグリニド（CYP2C8 の基質）0.5mg を単回経口投与したとき、レパグリニド単独投与時に対するセルペルカチニブカプセル併用投与時のレパグリニドの C_{max} 及び AUC_{inf} の幾何平均値の比は、1.91 及び 2.88 であった[15]（外国人データ）。［10.2 参照］

16.7.7 オメプラゾール

健康成人 20 例にオメプラゾール（プロトンポンプ阻害剤）40mg を 1 日 1 回反復経口投与し、セルペルカチニブカプセル 160mg を空腹時に単回経口投与したとき、セルペルカチニブカプセル単独投与時に対するオメプラゾール併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.123 及び 0.313 であった。また、オメプラゾールを反復経口投与し、セルペルカチニブカプセル 160mg を高脂肪食摂取後に単回経口投与したとき、セルペルカチニブカプセル単独投与時に対するオメプラゾール併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.586 及び 0.938 であった。オメプラゾールを反復経口投与し、セルペルカチニブカプセル 160mg を低脂肪食摂取後に単回経口投与したとき、セルペルカチニブカプセル単独投与時に対するオメプラゾール併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.782 及び 1.00 であった[5),16)]（外国人データ）。［10.2 参照］

16.7.8 ラニチジン

健康成人 20 例にラニチジン（H_2 受容体拮抗剤）150mg を 1 日 2 回反復経口投与し、セルペルカチニブカプセル 160mg をラニチジン投与 10 時間後及び 2 時間前に空腹時に単回経口投与したとき、セルペルカチニブカプセル単独投与時に対するラニチジン併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.818 及び 0.932 であった[16]（外国人データ）。［10.2 参照］

*16.7.9 ダビガトランエテキシラート

健康成人 35 例にセルペルカチニブカプセル 160mg 及びダビガトランエテキシラート（P-gp の基質）150mg を単回経口投与したとき、ダビガトランエテキシラート単独投与時に対するセルペルカチニブカプセル併用投与時のダビガトランの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.43 及び 1.38 であった[12),17)]（外国人データ）。［10.2 参照］

*16.7.10 ロスバスタチン

健康成人 28 例にセルペルカチニブカプセル 160mg 及びロスバスタチン（BCRP の基質）20mg を単回経口投与したとき、ロスバスタチン単独投与時に対するセルペルカチニブカプセル併用投与時のロスバスタチンの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.71 及び 1.80 であった[18]（外国人データ）。［10.2 参照］

*16.7.11 その他

(1) セルペルカチニブは MATE1 を阻害する（*in vitro*）[19]。

(2) 健康成人 12 例にリファンピシン（P-gp 阻害剤）600mg 及びセルペルカチニブカプセル 160mg を単回経口投与で併用したとき、セルペルカチニブカプセル単独投与時に対するリファンピシン併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.19 及び 1.06 であった[12]（外国人データ）。

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 国際共同第 I/II 相試験（LIBRETTO-001 試験）

〈*RET* 融合遺伝子陽性の進行・再発の非小細胞肺癌及び甲状腺癌、*RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌〉

①化学療法歴のある *RET* 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌患者 134 例（日本人患者 25 例を含む）及び②化学療法歴のない *RET* 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌患者 35 例（日本人患者 1 例を含む）にセルペルカチニブカプセル 1 回 160mg を 1 日 2 回経口投与した。主要評価項目である RECIST ver. 1.1 に基づく独立評価委員会判定による奏効率は、それぞれ①55.2%（95%信頼区間:46.4-63.8）及び②71.4%（95%信頼区間:53.7-85.4）であった。

12 歳以上の③化学療法歴のある *RET* 融合遺伝子陽性の根治切除不能な甲状腺癌患者 10 例[注 1)]（日本人患者 1 例を含む）、④化学療法歴のない *RET* 融合遺伝子陽性の根治切除不能な甲状腺癌患者 12 例[注 2)]、⑤化学療法歴のある *RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌患者 97 例（日本人患者 1 例を含む）及び⑥化学療法歴のない *RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌患者 90 例にセルペルカチニブカプセル 1 回 160mg[注 3)] を 1 日 2 回経口投与した。主要評価項目である RECIST ver. 1.1 に基づく独立評価委員会判定による奏効率は、それぞれ③50.0%（95%信頼区間:18.7-81.3）、④100%（95%信頼区間:73.5-100）、⑤68.0%（95%信頼区間:57.8-77.1）及び⑥63.3%（95%信頼区間:52.5-73.2）であった[3)]。（2020 年 3 月 30 日データカットオフ）［5.2、5.11 参照］

注 1）未分化癌 2 例、低分化癌 2 例を含む。

注 2）低分化癌 1 例を含む。

注 3）12 歳以上の小児に対する本剤の承認用法・用量は、(1) 体表面積 1.2m² 未満の患者に 80mg、(2) 体表面積 1.2m² 以上 1.6m² 未満の患者に 120mg、(3) 体表面積 1.6m² 以上の患者に 160mg を

それぞれ1日2回経口投与である。

安全性評価対象 400 例に認められた主な副作用は、口内乾燥（35.3%）、高血圧（31.8%）、ALT 増加（28.0%）、AST 増加（26.8%）、疲労（25.3%）等であった。（2020 年 3 月 30 日データカットオフ）

〈*RET*融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）〉

*RET*融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）患者として、セルペルカチニブカプセルの忍容性の評価を目的とした⑦第 I 相パート（セルペルカチニブカプセル 20mg を 1 日 1 回又はセルペルカチニブカプセル 1 回 20、40、60、80、120、160、200 若しくは 240mg を 1 日 2 回経口投与）[注4] の 5 例、セルペルカチニブカプセルの有効性及び安全性を検討することを目的とした第 II 相パート（セルペルカチニブカプセル 1 回 160mg を 1 日 2 回経口投与）のうち、⑧化学療法歴のある患者を対象としたコホートの 33 例（日本人患者 8 例を含む）、⑨化学療法歴のない患者を対象としたコホートの 2 例、⑩腫瘍組織検体以外で *RET* 融合遺伝子陽性が確認された患者等を対象としたコホートの 12 例（日本人患者 3 例を含む）が有効性の評価対象とされた。第 II 相パートの主要評価項目である RECIST ver. 1.1 に基づく独立評価委員会判定による奏効率は、それぞれ⑧57.6%（95%信頼区間:39.2-74.5）、⑨0%及び⑩16.7%であった[3]。（2023 年 1 月 13 日データカットオフ）［5.8 参照］

注 4）承認された用法・用量は本剤 1 回 160mg を 1 日 2 回経口投与である。

表 1）有効性の評価対象におけるがん種別の有効性

がん種	奏効例数/評価例数	奏効率
大腸癌	4/13	30.8%
膵癌[注5]	7/13	53.8%
唾液腺癌[注6]	2/4	50.0%
肉腫[注7]	1/3	33.3%
胆道癌[注6]	1/3	33.3%
原発不明癌	1/3	33.3%
黄色肉芽腫[注8]	0/2	0%
乳癌[注6]	2/2	100%
皮膚癌[注9]	1/2	50.0%
カルチノイド	1/1	100%
小腸癌	1/1	100%
直腸神経内分泌腫瘍[注10]	0/1	0%
卵巣癌	1/1	100%
肺癌肉腫	0/1	0%
神経内分泌癌	1/1	100%
小細胞肺癌	0/1	0%

注 5）セルペルカチニブカプセル 80mg を 1 日 2 回で投与が開始された患者 1 例を含む。
注 6）測定可能病変のない患者 1 例を含む。
注 7）紡錘形細胞肉腫、多形肉腫及び高悪性度胸部肉腫が組入れられ、紡錘形細胞肉腫において奏効が認められた。
注 8）いずれも測定可能病変のない患者
注 9）悪性黒色腫以外の皮膚癌（詳細不明）及び腺扁平上皮癌が組入れられ、悪性黒色腫以外の皮膚癌（詳細不明）において奏効が認められた。
注 10）セルペルカチニブカプセル 120mg を 1 日 2 回で投与が開始された患者

安全性評価対象 53 例に認められた主な副作用は、ALT 増加（35.8%）、AST 増加（28.3%）、口内乾燥（26.4%）、下痢（17.0%）、高血圧（17.0%）等であった。（2023 年 1 月 13 日データカットオフ）

***17.1.2 国際共同第 I/II 相試験（LIBRETTO-121 試験）（jRCT2080225127）**

*RET*遺伝子異常を有する進行・再発の固形腫瘍等の小児患者（生後 6 ヵ月以上 21 歳以下）を対象に、セルペルカチニブの有効性及び安全性を検討した。体表面積に合わせてセルペルカチニブ 1 回 92mg/m^2（最大投与量:160mg）を 1 日 2 回経口投与した[注11]。主要評価項目である RECIST ver. 1.1 に基づく独立評価委員会判定による奏効率は、有効性評価対象 36 例（日本人患者 3 例を含む）で 52.8%（95%信頼区間:35.5-69.6）であった[20]。（2024 年 11 月 8 日データカットオフ）［5.2、5.8、5.11 参照］

注 11）承認された用法・用量（小児）は、体表面積が 0.33m^{2}以上 0.66m^{2}未満の場合は 1 回 40mg を 1 日 3 回、0.66m^{2}以上 1.2m^{2}未満の場合は 1 回 80mg を 1 日 2 回、1.2m^{2}以上 1.6m^{2}未満の場合は 1 回 120mg を 1 日 2 回、1.6m^{2}以上の場合は 1 回 160mg を 1 日 2 回経口投与である。

表 2）有効性の評価対象におけるがん種別の有効性

がん種	奏効例数/評価例数	奏効率
甲状腺髄様癌[注12]	9/15[注15]	60.0%
甲状腺乳頭癌[注13]	8/15	53.3%
非甲状腺癌[注14]	2/6[注16]	33.3%

注 12）*RET*遺伝子変異陽性
注 13）*RET*融合遺伝子陽性
注 14）*RET*融合遺伝子陽性 3 例及び *RET*遺伝子変異陽性 3 例
注 15）*RET*融合遺伝子陽性の甲状腺髄様癌 1 例を含む。
注 16）乳児線維肉腫、悪性末梢神経鞘腫、骨肉腫、横紋筋肉腫、紡錘形細胞肉腫及び神経芽腫患者各 1 例が組み入れられ、うち、乳児線維肉腫及び紡錘形細胞肉腫患者において部分奏効が認められた。

安全性評価対象 36 例に認められた主な副作用は、AST 増加（36.1%）、ALT 増加（33.3%）、下痢（27.8%）、血中ビリルビン増加（25.0%）、血中アルカリホスファターゼ増加（19.4%）、疲労（19.4%）等であった。（2024 年 11 月 8 日データカットオフ）

17.3 その他

17.3.1 QT 間隔に対する影響

健康成人 32 例にセルペルカチニブカプセル 320 又は 640mg[注17]を単回経口投与したとき、QTc 間隔のベースラインからの変化量のプラセボとの差における 90%信頼区間の上限値は、それぞれ 11.87 及び 12.47msec であった[21]（外国人データ）。［8.2、9.1.1、11.1.2 参照］

注 17）成人に対する本剤の承認用法・用量は 160mg の 1 日 2 回経口投与である。

18. 薬効薬理

18.1 作用機序

セルペルカチニブは、RET、血管内皮増殖因子受容体（VEGFR）、線維芽細胞増殖因子受容体（FGFR）等のキナーゼ活性を阻害する。セルペルカチニブは、RET 融合タンパク等のリン酸化を阻害し、下流のシグナル伝達分子のリン酸化を阻害することにより、腫瘍増殖抑制作用を示すと考えられている[22]。

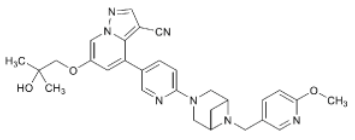
18.2 抗腫瘍効果

セルペルカチニブは、*in vitro* において、RET 融合タンパクを発現するヒト非小細胞肺癌由来 LC-2/ad 細胞株及びヒト甲状腺乳頭癌由来 TPC-1 細胞株並びに変異型 RET（C634W 及び M918T）をそれぞれ発現するヒト甲状腺髄様癌由来 TT 及び MZ-CRC1 細胞株に対して増殖抑制作用を示した。また、セルペルカチニブは、*in vivo* において、LC-2/ad 細胞株、RET 融合タンパクを発現する非小細胞肺癌患者由来 CTG-0838 腫瘍組織片及び TT 細胞株をそれぞれ皮下移植した重症複合型免疫不全-ベージュマウス又はヌードマウスにおいて、腫瘍増殖抑制作用を示した[22]。

19. 有効成分に関する理化学的知見

一般的名称:セルペルカチニブ（Selpercatinib）〔JAN〕
化学名:6-(2-Hydroxy-2-methylpropoxy)-4-(6-{6-[(6-methoxypyridin-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-3-yl}pyridin-3-yl)pyrazolo[1,5-*a*]pyridine-3-carbonitrile
分子式:$C_{29}H_{31}N_7O_3$
分子量:525.60
性状:白色～淡黄色の粉末である。0.1mol/L 塩酸にやや溶けにくく、アセトン及びエタノールに極めて溶けにくく、水にほとんど溶けない。

化学構造式:



融　　点:約 208℃

21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

〈*RET*融合遺伝子陽性の進行・再発の甲状腺癌、*RET*遺伝子変異陽性の根治切除不能な甲状腺髄様癌〉

21.2 国内での治験症例が極めて限られていることから、製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施することにより、本剤の使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを早期に収集し、本剤の適正使用に必要な措置を講じること。

22. 包装

〈レットヴィモカプセル 40mg〉

56 カプセル［8 カプセル（PTP）×7］

〈レットヴィモカプセル 80mg〉

56 カプセル［8 カプセル（PTP）×7］

23. 主要文献

1) 社内資料: セルペルカチニブの毒性試験(2022 年 2 月 25 日承認、CTD2.6.6)

2) 社内資料: セルペルカチニブのがん原性試験

3) 社内資料: 進行癌患者を対象としたセルペルカチニブの第 I/II 相試験(LOXO-RET-17001 試験)(2021 年 9 月 27 日承認、CTD2.7.2.4.2、2.7.6.12、審査報告書)(2022 年 2 月 25 日承認、審査報告書)

4) 社内資料: セルペルカチニブの絶対的バイオアベイラビリティ及びマスバランス試験(LOXO-RET-18016 試験)(2021 年 9 月 27 日承認、CTD2.7.6.3)

5) 社内資料: セルペルカチニブの薬物動態に及ぼす食事の影響及びオメプラゾールとの相互作用(LOXO-RET-18015 試験)(2021 年 9 月 27 日承認、CTD2.7.6.2)

6) 社内資料: セルペルカチニブのヒト血漿蛋白結合率(LOXO-292-DMPK-060 試験)(2021 年 9 月 27 日承認、CTD2.7.2.3.2)

7) 社内資料: セルペルカチニブのヒト血液中/血漿中濃度比(LOXO-292-DMPK-013 試験)(2021 年 9 月 27 日承認、CTD2.7.2.3.3)

8) 社内資料: セルペルカチニブの CYP 代謝(LOXO-292-DMPK-017 試験)(2021 年 9 月 27 日承認、CTD2.7.2.3.5)

9) 社内資料: 様々な重症度の腎機能障害を有する被験者におけるセルペルカチニブの薬物動態(LOXO-RET-18023 試験)(2021 年 9 月 27 日承認、CTD2.7.6.6)

10) 社内資料: 様々な重症度の肝機能障害を有する被験者におけるセルペルカチニブの薬物動態(LOXO-RET-18022 試験)(2021 年 9 月 27 日承認、CTD2.7.6.5)

*11) 社内資料: セルペルカチニブの母集団薬物動態解析及びシミュレーション

12) 社内資料: セルペルカチニブとイトラコナゾール及びリファンピシンの相互作用(LOXO-RET-18014 試験)(2021 年 9 月 27 日承認、CTD2.7.6.7)

13) 社内資料: セルペルカチニブの生理学的薬物動態モデル解析(LOXO-292-DMPK-052 試験)(2021 年 9 月 27 日承認、CTD2.7.2.2.12)

14) 社内資料: セルペルカチニブとミダゾラムの相互作用(LOXO-RET-18017 試験)(2021 年 9 月 27 日承認、CTD2.7.6.8)

15) 社内資料: セルペルカチニブとレパグリニドの相互作用(LOXO-RET-18026 試験)(2021 年 9 月 27 日承認、CTD2.7.6.9)

16) 社内資料: セルペルカチニブとラニチジン及びオメプラゾールの相互作用(LOXO-RET-19075 試験)(2021 年 9 月 27 日承認、CTD2.7.6.10)

*17) 社内資料: セルペルカチニブとダビガトランの相互作用試験(J2G-MC-JZJV 試験)

*18) 社内資料: セルペルカチニブとロスバスタチンの相互作用試験(J2G-MC-JZPB 試験)

19) 社内資料: セルペルカチニブによるトランスポータ阻害(LOXO-292-DMPK-035 試験)(2021 年 9 月 27 日承認、CTD2.7.2.3.8)

*20) 社内資料: 小児進行がん患者を対象としたセルペルカチニブの第 I/II 相試験(LOXO-RET-18036 試験)

21) 社内資料: セルペルカチニブの QT/QTc 評価(LOXO-RET-18032 試験)(2021 年 9 月 27 日承認、CTD2.7.2.2.8)

22) 社内資料: セルペルカチニブの薬理試験(2021 年 9 月 27 日承認、CTD2.6.2)

24. 文献請求先及び問い合わせ先

日本イーライリリー株式会社　医薬情報問合せ窓口
〒651-0086　神戸市中央区磯上通 5 丁目 1 番 28 号
TEL:0120-360-605（医療関係者向け）
medical.lilly.com/jp

26. 製造販売業者等

26.1 製造販売元

日本イーライリリー株式会社
神戸市中央区磯上通5丁目1番28号

Ⓡ:登録商標

RET-I001(Rx)

最新の添付文書を参照すること

*20xx 年 x 月改訂（第 x 版、用法及び用量変更）
2026 年 2 月改訂（第 3 版）

日本標準商品分類番号
874291

抗悪性腫瘍剤　RET 注 2) 受容体型チロシンキナーゼ阻害剤
セルペルカチニブ錠

貯　　法：室温保存
有効期間：36 ヵ月

レットヴィモ®錠40mg
レットヴィモ®錠80mg

Retevmo® Tablets

劇薬
処方箋医薬品注 1)
注 1）注意－医師等の処方箋により使用すること
注 2）RET ： rearranged during transfection

	40mg	80mg
承認番号	30700AMX00210	30700AMX00211
販売開始	2025 年 12 月	2025 年 12 月

1. 警告
本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）
本剤の成分に対しアナフィラキシー等の重篤な過敏症の既往歴のある患者

3. 組成・性状
3.1 組成

販売名	レットヴィモ錠 40mg	レットヴィモ錠 80mg
有効成分	1 錠中 セルペルカチニブ 40mg	1 錠中 セルペルカチニブ 80mg
添加剤	結晶セルロース、D-マンニトール、クロスカルメロースナトリウム、ヒドロキシプロピルセルロース、フマル酸ステアリルナトリウム、ポリビニルアルコール(部分けん化物)、酸化チタン、マクロゴール 4000、タルク、黒酸化鉄、三二酸化鉄(80mg のみ含有)	

3.2 製剤の性状

販売名		レットヴィモ錠 40mg	レットヴィモ錠 80mg
性状・剤形		明るい灰色の フィルムコーティング錠	暗赤紫色の フィルムコーティング錠
外形	表面		
	裏面		
	側面		
寸法・重量		直径：約 6mm 厚さ：約 3.47mm 重量：約 104.7mg	直径：約 7.3mm 厚さ：約 4.61mm 重量：約 207.4mg
識別コード		Ret 40 5340	Ret 80 6082

4. 効能又は効果
○*RET* 融合遺伝子陽性の進行・再発の固形腫瘍
○*RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌

5. 効能又は効果に関連する注意
〈*RET* 融合遺伝子陽性の進行・再発の非小細胞肺癌〉
5.1 十分な経験を有する病理医又は検査施設における検査により、*RET* 融合遺伝子陽性が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器注) を用いること。
*5.2 「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。[17.1.1、17.1.2 参照]
5.3 本剤の術後補助療法における有効性及び安全性は確立していない。
〈*RET* 融合遺伝子陽性の進行・再発の甲状腺癌〉
5.4 十分な経験を有する病理医又は検査施設における検査により、*RET* 融合遺伝子陽性が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器注) を用いること。
5.5 放射性ヨウ素による治療の適応となる患者においては、当該治療を優先すること。
〈*RET* 融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）〉
5.6 十分な経験を有する病理医又は検査施設における検査により、*RET* 融合遺伝子陽性が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器注) を用いること。
5.7 組織球症患者は本剤の投与対象となり得る。
*5.8 臨床試験に組み入れられた患者のがん種等について、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。[17.1.1、17.1.2 参照]
5.9 本剤の手術の補助療法における有効性及び安全性は確立していない。
〈*RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌〉
5.10 十分な経験を有する病理医又は検査施設における検査により、*RET* 遺伝子変異が確認された患者に投与すること。生殖細胞系列の *RET* 遺伝子変異が陰性又は不明の場合は、承認された体外診断用医薬品又は医療機器注) を用いて検査を行うこと。
*5.11 「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。[17.1.1、17.1.2 参照]

注）承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

*6. 用法及び用量
通常、成人にはセルペルカチニブとして 1 回 160mg を 1 日 2 回経口投与する。なお、患者の状態により適宜減量する。
通常、2 歳以上の小児には体表面積に合わせて次の投与量（セルペルカチニブとして 1 日量約 184mg/m²）を経口投与する。なお、患者

の状態により適宜減量する。

小児の用量

体表面積	投与量
0.33㎡以上 0.66㎡未満	1回 40mg　1日3回
0.66㎡以上 1.2㎡未満	1回 80mg　1日2回
1.2㎡以上 1.6㎡未満	1回 120mg　1日2回
1.6㎡以上	1回 160mg　1日2回

7. 用法及び用量に関連する注意

7.1 他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。

*7.2 本剤投与により副作用が発現した場合には、以下の基準を考慮して、休薬・減量・中止すること。

成人の場合　本剤の減量の目安

減量レベル	投与量
通常投与量	1回 160mg　1日2回
1段階減量	1回 120mg　1日2回
2段階減量	1回 80mg　1日2回
3段階減量	1回 40mg　1日2回

小児の場合　本剤の減量の目安

体表面積	減量レベル	投与量
0.33㎡以上 0.66㎡未満	通常投与量	1回 40mg　1日3回
	1段階減量	1回 40mg　1日2回
	2段階減量	1回 40mg　1日1回
	3段階減量	投与中止
0.66㎡以上 1.2㎡未満	通常投与量	1回 80mg　1日2回
	1段階減量	1回 40mg　1日2回
	2段階減量	1回 40mg　1日1回
	3段階減量	投与中止
1.2㎡以上 1.6㎡未満	通常投与量	1回 120mg　1日2回
	1段階減量	1回 80mg　1日2回
	2段階減量	1回 40mg　1日1回 及び1回 80mg　1日1回 (1日量 120mg)
	3段階減量 a)	1回 40mg　1日1回
1.6㎡以上	通常投与量	1回 160mg　1日2回
	1段階減量	1回 120mg　1日2回
	2段階減量	1回 80mg　1日2回
	3段階減量	1回 40mg　1日2回

a) 過敏症発現時のみ（過敏症以外で2段階減量において忍容性が得られない場合、投与中止）

副作用に対する休薬、減量及び中止基準

副作用	程度 a)	処置
ALT又はAST増加	グレード3又は4	グレード1以下に回復するまで休薬し、回復後は2段階減量して投与再開できる。 再開後に2週間以上再発しない場合には、1段階増量することができる。更に4週間以上再発しない場合には、もう1段階増量することができる。 減量した用量で投与中に再発した場合には、中止する。
QT間隔延長	QTc間隔>500msec	QTc間隔<470msecに回復するまで休薬し、回復後は1段階減量して投与再開できる。 2段階減量した用量で投与中に再発した場合には、中止する。
	重篤な不整脈を疑う所見や症状が認められた場合	中止する。
高血圧	グレード3又は4	回復するまで休薬し、回復後は1段階減量して投与再開できる。
過敏症(アナフィラキシー等の重篤な過敏症を除く) [11.1.3参照]	グレード1～4	回復するまで休薬し、副腎皮質ステロイドの全身投与を考慮する。回復後は副腎皮質ステロイドを併用しながら3段階減量して投与再開できる。 再開後に7日以上再発しない場合には、1段階ずつ発現時の用量まで増量できる。増量後に7日以上再発しない場合には、副腎皮質ステロイドを漸減する。
間質性肺疾患	グレード2	回復するまで休薬し、回復後は1段階減量して投与再開できる。
	グレード3又は4	中止する。
上記以外の副作用	グレード3又は4	回復するまで休薬し、回復後は1段階減量して投与再開できる。

a) グレードはNCI-CTCAE ver. 4.03に準じる。
b) 体表面積1.2㎡以上の場合のみ

8. 重要な基本的注意

8.1 肝機能障害があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に肝機能検査を行い、患者の状態を十分に観察すること。[11.1.1参照]

*8.2 QT間隔延長があらわれることがあるので、本剤の投与開始前には患者のQTc間隔が成人470msec、12歳未満の小児440msec以下であることを確認するとともに血清電解質検査（カリウム、マグネシウム等）を行うこと。心電図及び血清電解質検査を投与開始後1週間時点及び投与開始後6ヵ月間は毎月1回行い、以降も必要に応じて行うこと。また、必要に応じて電解質補正を行うこと。[11.1.2、17.3.1参照]

8.3 高血圧があらわれることがあるので、本剤の投与開始前に血圧が適切に管理されていることを確認すること。本剤投与中は定期的に血圧を測定すること。

8.4 間質性肺疾患があらわれることがあるので、本剤の投与にあたっては、初期症状（呼吸困難、咳嗽、発熱等）の確認及び胸部画像検査の実施等、患者の状態を十分に観察すること。また、患者に副作用について説明するとともに、間質性肺疾患の初期症状が発現した場合には、速やかに医療機関を受診するよう説明すること。[9.1.3、11.1.5参照]

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 QT間隔延長のおそれ又はその既往歴のある患者

QT間隔延長が発現するおそれがある。先天性/後天性QT延長症候群又はその他不整脈の要因になる病態を有する患者には慎重に投与すること。[11.1.2、17.3.1参照]

9.1.2 高血圧症の患者

高血圧が悪化するおそれがある。[11.1.4参照]

9.1.3 間質性肺疾患のある患者又はその既往歴のある患者

間質性肺疾患が発現又は増悪するおそれがある。[8.4、11.1.5参照]

9.3 肝機能障害患者

9.3.1 重度の肝機能障害のある患者（Child-Pugh分類C）

減量を考慮するとともに、患者の状態をより慎重に観察し、副作用の発現に十分注意すること。本剤の血中濃度が上昇し、副作用が増強されるおそれがある。[16.6.2参照]

9.4 生殖能を有する者

9.4.1 妊娠する可能性のある女性には、本剤投与中及び最終投与後1ヵ月間において避妊する必要性及び適切な避妊法について説明すること。[9.5参照]

9.4.2 男性には、本剤投与中及び最終投与後1週間においてバリア法（コンドーム）を用いて避妊する必要性について説明すること。[15.2.1参照]

9.4.3 成長期にある若年男性又は男児に投与する場合には、造精機能の低下があらわれる可能性があることを考慮すること。幼若ラットにおいて、精巣の精上皮変性、精巣上体の精子枯渇、精子運動率低値、異常形態精子比率高値及び受胎能の低下が認められ、精巣及び精巣上体の所見に回復性は認められていない[1)]。

9.5 妊婦

妊婦又は妊娠している可能性のある女性には治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。ラットを用いた胚・胎児発生毒性試験において、臨床曝露量（AUC）と同程度の曝露量で胎児死亡及び奇形が認められている[1)]。[9.4.1参照]

9.6 授乳婦
授乳しないことが望ましい。乳汁移行に関するデータはないが、本剤はBCRPの基質であるため、乳汁移行の可能性がある。

9.7 小児等
9.7.1 成長期にある若年者においては、骨成長について以下の点に注意すること。
・骨端線に異常がないか十分に観察すること。骨端線に異常が認められた場合には、投与継続の可否を慎重に判断すること。
・関節痛及び歩行障害について十分に観察すること。大腿骨頭すべり症等の骨端離開があらわれることがある。
［15.2.2 参照］

9.7.2 2歳未満の小児等を対象とした臨床試験は実施していない。

*10. 相互作用
本剤は、主にCYP3A4によって代謝され、CYP2C8、CYP3A、P-gp及びBCRPの阻害作用を示す。また、本剤の溶解度はpHの上昇により低下する。

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
CYP2C8の基質となる薬剤 レパグリニド ピオグリタゾン モンテルカスト等 ［16.7.6 参照］	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤がCYP2C8を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。
CYP3Aの基質となる薬剤 ミダゾラム トリアゾラム ロミタピド等 ［16.7.5 参照］	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤がCYP3Aを阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。
CYP3A阻害剤 イトラコナゾール クラリスロマイシン エリスロマイシン等 ［16.7.1、16.7.2 参照］	本剤の副作用が増強されるおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤の減量を考慮するとともに、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	これらの薬剤がCYP3Aを阻害することにより、本剤の血中濃度が上昇する可能性がある。
CYP3A誘導剤 リファンピシン フェニトイン ボセンタン等 ［16.7.3、16.7.4 参照］	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避け、CYP3A誘導作用のない薬剤への代替を考慮すること。	これらの薬剤等がCYP3Aを誘導することにより、本剤の血中濃度が低下する可能性がある。
セイヨウオトギリソウ(St. John's Wort、セント・ジョーンズ・ワート)含有製品	本剤の有効性が減弱するおそれがあるので、摂取しないよう注意すること。	
プロトンポンプ阻害剤 オメプラゾール ランソプラゾール エソメプラゾール等 ［16.7.7 参照］	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤とともに食後に投与すること。	これらの薬剤による胃内pHの上昇により、本剤の吸収が低下し、本剤の血中濃度が低下する可能性がある。
H_2受容体拮抗剤 ラニチジン ファモチジン シメチジン等 ［16.7.8 参照］	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤と服用時間をずらすこと(ラニチジンを本剤投与10時間前及び2時間後に投与したときの本剤の血中濃度への影響は限定的であった)。	
制酸剤 炭酸カルシウム 水酸化マグネシウム 水酸化アルミニウム等	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤と服用時間をずらすこと(制酸剤を本剤投与2時間前又は2時間後に投与したときの本剤の血中濃度への影響は限定的であった)。	
治療域の狭いP-gpの基質となる薬剤 ジゴキシン シロリムス エベロリムス等 ［16.7.9 参照］	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤がP-gpを阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。
BCRPの基質となる薬剤 ロスバスタチン メトトレキサート イマチニブ等 ［16.7.10 参照］		本剤がBCRPを阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。

11. 副作用
次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用
***11.1.1 肝機能障害**（37.8%）
［8.1 参照］

11.1.2 QT間隔延長（13.9%）
［8.2、9.1.1、17.3.1 参照］

***11.1.3 過敏症**（4.9%）
発疹、発熱等の症状を伴う遅発性の過敏症があらわれることがある。［7.2 参照］

***11.1.4 高血圧**（28.0%）
［9.1.2 参照］

***11.1.5 間質性肺疾患**（0.6%）
［8.4、9.1.3 参照］

11.2 その他の副作用

副作用分類	20%以上	5～20%未満	5%未満	頻度不明
*消化器	口内乾燥(31.9%)、下痢	便秘、悪心、口内炎、腹痛	嘔吐	
*一般・全身及び投与部位反応	疲労	浮腫	発熱	
呼吸器			鼻出血、肺炎	
感染症			尿路感染	
内分泌			甲状腺機能低下症	
代謝・栄養障害		食欲減退		
精神神経系		頭痛	浮動性めまい	
皮膚		発疹		
生殖器		勃起不全		
血液		血小板減少、白血球減少、好中球減少	リンパ球減少、貧血	
*臨床検査値異常		血中クレアチニン増加	低マグネシウム血症、低アルブミン血症、低カリウム血症、低カルシウム血症	
*その他			乳び腹水	乳び胸

14. 適用上の注意
14.1 薬剤交付時の注意
PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。PTPシートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。

15. その他の注意
15.2 非臨床試験に基づく情報
15.2.1 セルペルカチニブは、ラット小核試験において、臨床用量160mg1日2回で得られるC_{max}の5.2倍に相当する用量で遺伝毒性が陽性であった[1)]。［9.4.2 参照］

15.2.2 動物試験（成長板が閉鎖していない幼若ラット、若齢ラット及び若齢ミニブタ）において、本剤の反復投与により骨端成長板の異常(骨端軟骨の肥大、過形成及び異形成)が、ヒトに160mg1日2回の用量で投与したときの臨床曝露量よりも低い曝露量で

認められている。また、幼若ラットにおいて、骨端成長板の変化に関連して、骨密度及び大腿骨長の低値が、ヒトに 160mg1 日 2 回の用量で投与したときの臨床曝露量のそれぞれ 0.8 倍及び 1.9 倍で認められている[1]。[9.7.1 参照]

15.2.3 ラットを用いた 2 年間がん原性試験において、ヒトに 160mg1 日 2 回の用量で投与したときの臨床曝露量に相当する用量で雌に膣腫瘍が認められている[2]。

16. 薬物動態

16.1 血中濃度

16.1.1 単回及び反復投与

進行固形腫瘍患者 94 例にセルペルカチニブカプセル 160mg を単回経口投与したときの血漿中濃度推移及び薬物動態パラメータは以下のとおりであった[3]（外国人データ）。

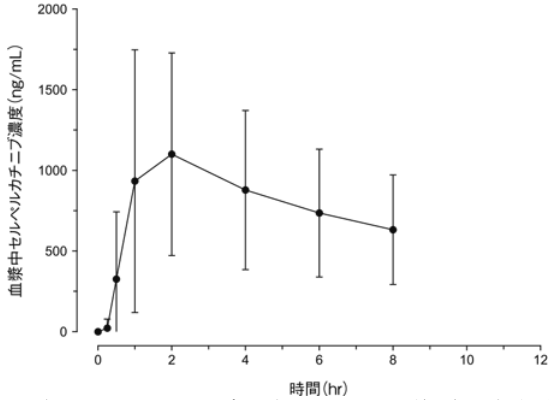


図 1）セルペルカチニブカプセル 160mg を単回経口投与後（第 1 サイクル第 1 日目）の血漿中濃度推移（平均値±標準偏差）

表 1）セルペルカチニブカプセル 160mg を単回経口投与後（第 1 サイクル第 1 日目）の薬物動態パラメータ（幾何平均値及び変動係数%）

例数	94
C_{max} (ng/mL)	1120 (85.7)
t_{max}[a] (hr)	1.96 (0.50-7.83)
AUC_{τ} (ng・hr/mL)	7430[b] (67.5)

a）中央値（最小値-最大値）
b）例数=71
τ：投与間隔（12 時間）

日本人の進行固形腫瘍患者 58 例にセルペルカチニブカプセル 160mg を 1 日 2 回反復経口投与したときの定常状態における血漿中濃度推移及び薬物動態パラメータは以下のとおりであった[3]。

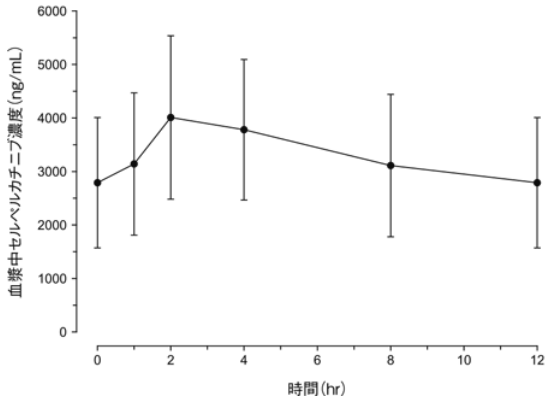


図 2）セルペルカチニブカプセル 160mg を 1 日 2 回反復経口投与後（第 1 サイクル第 8 日目）の定常状態における血漿中濃度推移（平均値±標準偏差）

表 2）セルペルカチニブカプセル 160mg を 1 日 2 回反復経口投与後（第 1 サイクル第 8 日目）の定常状態における薬物動態パラメータ（幾何平均値及び変動係数%）

例数	58
$C_{max,ss}$ (ng/mL)	4060 (34.4)
$t_{max,ss}$[a] (hr)	2.08 (0.00-8.10)
$AUC_{\tau,ss}$ (ng・hr/mL)	37100 (39.3)
CL_{ss}/F (L/hr)	4.31 (39.3)

a）中央値（最小値-最大値）
τ：投与間隔（12 時間）

血漿中濃度は反復投与後 8 日までに定常状態に到達した。また、セルペルカチニブカプセル 160mg を 1 日 2 回反復経口投与した際の投与 8 日目におけるセルペルカチニブの蓄積率は 3.40 であった。

16.1.2 生物学的同等性

健康成人 224 例にセルペルカチニブ 160mg 錠（国内未承認）を 1 錠又はセルペルカチニブ 80mg カプセルを 2 カプセル空腹時単回経口投与したとき、錠剤はカプセルと生物学的に同等であることが確認された[4]（外国人データ）。

表 3）セルペルカチニブ 160mg を錠剤又はカプセルで空腹時単回経口投与したときの薬物動態パラメータ（幾何平均値及び変動係数%）

投与	t_{max}[a] (hr)	C_{max} (ng/mL)	AUC_{0-t} (ng・hr/mL)
160mg 錠	1.50[b] (0.75-36.0)	1350[b] (91)	18100[c] (65)
80mg カプセル x2	1.50[d] (0.75-36.0)	1520[d] (61)	20200[b] (47)

a）中央値（最小値-最大値）
b）例数=206
c）例数=204
d）例数=209

16.2 吸収

16.2.1 絶対的バイオアベイラビリティ

健康成人 6 例にセルペルカチニブカプセル 160mg を単回経口投与したときの絶対的バイオアベイラビリティの幾何平均値は 73.2%であった[5]（外国人データ）。

16.2.2 食事の影響

健康成人 46 例にセルペルカチニブ錠 160mg（国内未承認）を高脂肪食摂取後に単回経口投与したとき、空腹時投与に対する食後投与におけるセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比はそれぞれ 0.829 及び 0.952 であった[6]（外国人データ）。

16.3 分布

16.3.1 蛋白結合率

セルペルカチニブのヒト血漿タンパク結合率は約 96%であり、濃度依存性は認められなかった（*in vitro*）[7]。

16.3.2 血液/血漿中濃度比

セルペルカチニブの血液/血漿中濃度比は約 0.7 であった（*in vitro*）[8]。

16.4 代謝

セルペルカチニブは主として CYP3A4 により代謝される（*in vitro*）[9]。健康成人 6 例に［^{14}C］-セルペルカチニブ 160mg を単回経口投与したとき、投与 168 時間後までの血漿中には主に未変化体が検出された（血漿中総放射能に対する割合は、86.2%）[5]（外国人データ）。

16.5 排泄

健康成人 6 例に［^{14}C］-セルペルカチニブ 160mg を単回経口投与したとき、投与 432 時間後までに投与した放射能の約 69%（未変化体は約 14%）が糞便中に排泄され、約 24%（未変化体は約 11.5%）が尿中に排泄された[5]（外国人データ）。

16.6 特定の背景を有する患者

16.6.1 腎機能障害患者

セルペルカチニブカプセル 160mg を単回経口投与したとき、腎機能正常被験者（10 例）に対する軽度の腎機能障害患者（8 例）の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.30 及び 1.07 であった。腎機能正常被験者（10 例）に対する中等度の腎機能障害患者（8 例）の非結合形セルペ

ルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.67 及び 1.89 であった。腎機能正常被験者（10 例）に対する重度の腎機能障害患者（7 例）の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.04 及び 1.54 であった[10]（外国人データ）。血液透析の有無によらず、末期腎不全患者に関するデータはない。

16.6.2 肝機能障害患者

セルペルカチニブカプセル 160mg を単回経口投与したとき、肝機能正常被験者（12 例）に対する軽度の肝機能障害患者（8 例）の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.78 及び 1.33 であった。肝機能正常被験者（12 例）に対する中等度の肝機能障害患者（8 例）の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 0.989 及び 0.991 であった。肝機能正常被験者（12 例）に対する重度の肝機能障害患者（8 例）の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 2.32 及び 3.28 であった[11]（外国人データ）。［9.3.1 参照］

***16.6.3 小児**

国際共同第 I/II 相試験（LIBRETTO-001 試験及び LIBRETTO-121 試験）に組み入れられた 839 例（18 歳未満の患者 34 例を含む）のデータを用いて母集団薬物動態モデルを構築した。年齢によりセルペルカチニブの薬物動態に臨床的に意味のある差は認められなかったが、体重の増加に伴いセルペルカチニブの V_{ss}/F 及び CL/F は増加した。母集団薬物動態モデルを用いて、仮想患者の体表面積及び体重情報に基づく薬物動態シミュレーションを実施した結果、①体表面積 0.33m^2 以上 0.66m^2 未満の患者に 40mg1 日 3 回、②体表面積 0.66m^2 以上 1.2m^2 未満の患者に 80mg1 日 2 回、③体表面積 1.2m^2 以上 1.6m^2 未満の患者に 120mg1 日 2 回、④体表面積 1.6m^2 以上の患者に 160mg1 日 2 回をそれぞれ反復経口投与した際の、定常状態におけるセルペルカチニブの C_{max}（ng/mL）及び AUC_{24h}（ng・hr/mL）の中央値は、①3120 及び 57700、②3360 及び 58300、③3190 及び 58600 並びに④3550 及び 66400 と推定された[12]。

16.7 薬物相互作用

16.7.1 イトラコナゾール

健康成人 12 例にイトラコナゾール（強い CYP3A 阻害剤）200mg を 1 日 1 回反復経口投与し、セルペルカチニブカプセル 160mg を単回経口投与したとき、セルペルカチニブカプセル単独投与時に対するイトラコナゾール併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、1.30 及び 2.33 であった[13]（外国人データ）。［10.2 参照］

16.7.2 フルコナゾール、ジルチアゼム

生理学的薬物動態モデルに基づいたシミュレーションにおいて、セルペルカチニブカプセル（160mg を単回経口投与）単独投与時に対するフルコナゾール（中程度の CYP3A 阻害剤）（200mg を 1 日 1 回反復経口投与）併用投与時のセルペルカチニブの C_{max} 及び AUC の幾何平均値の比は、それぞれ 1.20 及び 2.48 と推定された。セルペルカチニブカプセル（160mg を単回経口投与）単独投与時に対するジルチアゼム（中程度の CYP3A 阻害剤）（60mg を 1 日 3 回反復経口投与）併用投与時のセルペルカチニブの C_{max} 及び AUC の幾何平均値の比は、それぞれ 1.17 及び 2.18 と推定された[14]。［10.2 参照］

16.7.3 リファンピシン

健康成人 12 例にリファンピシン（強い CYP3A 誘導剤）600mg を 1 日 1 回反復経口投与し、セルペルカチニブカプセル 160mg を単回経口投与したとき、セルペルカチニブカプセル単独投与時に対するリファンピシン併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.301 及び 0.133 であった[13]（外国人データ）。［10.2 参照］

16.7.4 ボセンタン、モダフィニル

生理学的薬物動態モデルに基づいたシミュレーションにおいて、セルペルカチニブカプセル（160mg を単回経口投与）単独投与時に対するボセンタン（中程度の CYP3A 誘導剤）（125mg を 1 日 2 回反復経口投与）併用投与時のセルペルカチニブの C_{max} 及び AUC の幾何平均値の比は、それぞれ 0.71 及び 0.53 と推定された。セルペルカチニブカプセル（160mg を単回経口投与）単独投与時に対するモダフィニル（中程度の CYP3A 誘導剤）（200mg を 1 日 1 回 7 日間経口投与後に 400mg を 1 日 1 回反復経口投与）併用投与時のセルペルカチニブの C_{max} 及び AUC の幾何平均値の比は、それぞれ 0.86 及び 0.64 と推定された[14]。［10.2 参照］

16.7.5 ミダゾラム

健康成人 16 例にセルペルカチニブカプセル 160mg を 1 日 2 回反復経口投与し、ミダゾラム（CYP3A の基質）2mg を単回経口投与したとき、ミダゾラム単独投与時に対するセルペルカチニブカプセル併用投与時のミダゾラムの C_{max} 及び AUC_{inf} の幾何平均値の比は、1.39 及び 1.54 であった[15]（外国人データ）。［10.2 参照］

16.7.6 レパグリニド

健康成人 16 例にセルペルカチニブカプセル 160mg を 1 日 2 回反復経口投与し、レパグリニド（CYP2C8 の基質）0.5mg を単回経口投与したとき、レパグリニド単独投与時に対するセルペルカチニブカプセル併用投与時のレパグリニドの C_{max} 及び AUC_{inf} の幾何平均値の比は、1.91 及び 2.88 であった[16]（外国人データ）。［10.2 参照］

16.7.7 オメプラゾール

健康成人 20 例にオメプラゾール（プロトンポンプ阻害剤）40mg を 1 日 1 回反復経口投与し、セルペルカチニブカプセル 160mg を空腹時に単回経口投与したとき、セルペルカチニブカプセル単独投与時に対するオメプラゾール併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.123 及び 0.313 であった。また、オメプラゾールを反復経口投与し、セルペルカチニブカプセル 160mg を高脂肪食摂取後に単回経口投与したとき、セルペルカチニブカプセル単独投与時に対するオメプラゾール併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.586 及び 0.938 であった。オメプラゾールを反復経口投与し、セルペルカチニブカプセル 160mg を低脂肪食摂取後に単回経口投与したとき、セルペルカチニブカプセル単独投与時に対するオメプラゾール併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.782 及び 1.00 であった[17),18)]（外国人データ）。［10.2 参照］

16.7.8 ラニチジン

健康成人 20 例にラニチジン（H_2 受容体拮抗剤）150mg を 1 日 2 回反復経口投与し、セルペルカチニブカプセル 160mg をラニチジン投与 10 時間後及び 2 時間前に空腹時に単回経口投与したとき、セルペルカチニブカプセル単独投与時に対するラニチジン併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.818 及び 0.932 であった[18]（外国人データ）。［10.2 参照］

***16.7.9 ダビガトランエテキシラート**

健康成人 35 例にセルペルカチニブカプセル 160mg 及びダビガトランエテキシラート（P-gp の基質）150mg を単回経口投与したとき、ダビガトランエテキシラート単独投与時に対するセルペルカチニブカプセル併用投与時のダビガトランの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.43 及び 1.38 であった[13),19)]（外国人データ）。［10.2 参照］

***16.7.10 ロスバスタチン**

健康成人 28 例にセルペルカチニブカプセル 160mg 及びロスバスタチン（BCRP の基質）20mg を単回経口投与したとき、ロスバスタチン単独投与時に対するセルペルカチニブカプセル併用投与時のロスバスタチンの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.71 及び 1.80 であった[20]（外国人データ）。［10.2 参照］

***16.7.11 その他**

(1) セルペルカチニブは MATE1 を阻害する（*in vitro*）[21]。

(2) 健康成人 12 例にリファンピシン（P-gp 阻害剤）600mg 及びセルペルカチニブカプセル 160mg を単回経口投与で併用したとき、セルペルカチニブカプセル単独投与時に対するリファンピシン併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.19 及び 1.06 であった[13]（外国人データ）。

16.8 その他

本剤 40mg 及び 80mg は、「含量が異なる経口固形製剤の生物学的同等性試験ガイドライン（令和 2 年 3 月 19 日薬生薬審発 0319 第 1 号）」に基づき、本剤 160mg（国内未承認）を標準製剤としたとき、溶出挙動が同等と判断され、生物学的に同等とみなされた。

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 国際共同第 I/II 相試験（LIBRETTO-001 試験）

〈*RET* 融合遺伝子陽性の進行・再発の非小細胞肺癌及び甲状腺癌、*RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌〉

①化学療法歴のある *RET* 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌患者 134 例（日本人患者 25 例を含む）及び②化学療法歴のない *RET* 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌患者 35 例（日本人患者 1 例を含む）にセルペル

カチニブカプセル 1 回 160mg を 1 日 2 回経口投与した。主要評価項目である RECIST ver. 1.1 に基づく独立評価委員会判定による奏効率は、それぞれ①55.2%（95%信頼区間:46.4-63.8）及び②71.4%（95%信頼区間:53.7-85.4）であった。
12 歳以上の③化学療法歴のある *RET* 融合遺伝子陽性の根治切除不能な甲状腺癌患者 10 例[注1)]（日本人患者 1 例を含む）、④化学療法歴のない *RET* 融合遺伝子陽性の根治切除不能な甲状腺癌患者 12 例[注2)]、⑤化学療法歴のある *RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌患者 97 例（日本人患者 1 例を含む）及び⑥化学療法歴のない *RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌患者 90 例にセルペルカチニブカプセル 1 回 160mg[注3)] を 1 日 2 回経口投与した。主要評価項目である RECIST ver. 1.1 に基づく独立評価委員会判定による奏効率は、それぞれ③50.0%（95%信頼区間:18.7-81.3）、④100%（95%信頼区間:73.5-100）、⑤68.0%（95%信頼区間:57.8-77.1）及び⑥63.3%（95%信頼区間:52.5-73.2）であった[3)]。（2020 年 3 月 30 日データカットオフ）［5.2、5.11 参照］
注 1）未分化癌 2 例、低分化癌 2 例を含む。
注 2）低分化癌 1 例を含む。
注 3）12 歳以上の小児に対する本剤の承認用法・用量は、(1) 体表面積 1.2m^2 未満の患者に 80mg、(2) 体表面積 1.2m^2 以上 1.6m^2 未満の患者に 120mg、(3) 体表面積 1.6m^2 以上の患者に 160mg をそれぞれ 1 日 2 回経口投与である。

安全性評価対象 400 例に認められた主な副作用は、口内乾燥（35.3%）、高血圧（31.8%）、ALT 増加（28.0%）、AST 増加（26.8%）、疲労（25.3%）等であった。（2020 年 3 月 30 日データカットオフ）

〈*RET* 融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）〉
RET 融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）患者として、セルペルカチニブカプセルの忍容性の評価を目的とした⑦第 I 相パート（セルペルカチニブカプセル 20mg を 1 日 1 回又はセルペルカチニブカプセル 1 回 20、40、60、80、120、160、200 若しくは 240mg を 1 日 2 回経口投与）[注4)] の 5 例、セルペルカチニブカプセルの有効性及び安全性を検討することを目的とした第 II 相パート（セルペルカチニブカプセル 1 回 160mg を 1 日 2 回経口投与）のうち、⑧化学療法歴のある患者を対象としたコホートの 33 例（日本人患者 8 例を含む）、⑨化学療法歴のない患者を対象としたコホートの 2 例、⑩腫瘍組織検体以外で *RET* 融合遺伝子陽性が確認された患者等を対象としたコホートの 12 例（日本人患者 3 例を含む）が有効性の評価対象とされた。第 II 相パートの主要評価項目である RECIST ver. 1.1 に基づく独立評価委員会判定による奏効率は、それぞれ⑧57.6%（95%信頼区間:39.2-74.5）、⑨0%及び⑩16.7%であった[3)]。（2023 年 1 月 13 日データカットオフ）［5.8 参照］
注 4）承認された用法・用量は本剤 1 回 160mg を 1 日 2 回経口投与である。

表 1）有効性の評価対象におけるがん種別の有効性

がん種	奏効例数/評価例数	奏効率
大腸癌	4/13	30.8%
膵癌[a)]	7/13	53.8%
唾液腺癌[b)]	2/4	50.0%
肉腫[c)]	1/3	33.3%
胆道癌[b)]	1/3	33.3%
原発不明癌	1/3	33.3%
黄色肉芽腫[d)]	0/2	0%
乳癌[b)]	2/2	100%
皮膚癌[e)]	1/2	50.0%
カルチノイド	1/1	100%
小腸癌	1/1	100%
直腸神経内分泌腫瘍[f)]	0/1	0%
卵巣癌	1/1	100%
肺癌肉腫	0/1	0%
神経内分泌癌	1/1	100%
小細胞肺癌	0/1	0%

a）セルペルカチニブカプセル 80mg を 1 日 2 回で投与が開始された患者 1 例を含む。
b）測定可能病変のない患者 1 例を含む。
c）紡錘形細胞肉腫、多形肉腫及び高悪性度胸部肉腫が組入れられ、紡錘形細胞肉腫において奏効が認められた。
d）いずれも測定可能病変のない患者
e）悪性黒色腫以外の皮膚癌（詳細不明）及び腺扁平上皮癌が組入れられ、悪性黒色腫以外の皮膚癌（詳細不明）において奏効が認められた。
f）セルペルカチニブカプセル 120mg を 1 日 2 回で投与が開始された患者

安全性評価対象 53 例に認められた主な副作用は、ALT 増加（35.8%）、AST 増加（28.3%）、口内乾燥（26.4%）、下痢（17.0%）、高血圧（17.0%）等であった。（2023 年 1 月 13 日データカットオフ）

***17.1.2 国際共同第 I/II 相試験（LIBRETTO-121 試験）（jRCT2080225127）**
RET 遺伝子異常を有する進行・再発の固形腫瘍等の小児患者（生後 6 ヵ月以上 21 歳以下）を対象に、セルペルカチニブの有効性及び安全性を検討した。体表面積に合わせてセルペルカチニブ 1 回 92mg/m^2（最大投与量:160mg）を 1 日 2 回経口投与した[注5)]。主要評価項目である RECIST ver. 1.1 に基づく独立評価委員会判定による奏効率は、有効性評価対象 36 例（日本人患者 3 例を含む）で 52.8%（95%信頼区間:35.5-69.6）であった[22)]。（2024 年 11 月 8 日データカットオフ）［5.2、5.8、5.11 参照］

注 5）承認された用法・用量（小児）は、体表面積が 0.33m^2 以上 0.66m^2 未満の場合は 1 回 40mg を 1 日 3 回、0.66m^2 以上 1.2m^2 未満の場合は 1 回 80mg を 1 日 2 回、1.2m^2 以上 1.6m^2 未満の場合は 1 回 120mg を 1 日 2 回、1.6m^2 以上の場合は 1 回 160mg を 1 日 2 回経口投与である。

表 2）有効性の評価対象におけるがん種別の有効性

がん種	奏効例数/評価例数	奏効率
甲状腺髄様癌[a)]	9/15[d)]	60.0%
甲状腺乳頭癌[b)]	8/15	53.3%
非甲状腺癌[c)]	2/6[e)]	33.3%

a）*RET* 遺伝子変異陽性
b）*RET* 融合遺伝子陽性
c）*RET* 融合遺伝子陽性 3 例及び *RET* 遺伝子変異陽性 3 例
d）*RET* 融合遺伝子陽性の甲状腺髄様癌 1 例を含む。
e）乳児線維肉腫、悪性末梢神経鞘腫、骨肉腫、横紋筋肉腫、紡錘形細胞肉腫及び神経芽腫患者各 1 例が組み入れられ、うち、乳児線維肉腫及び紡錘形細胞肉腫患者において部分奏効が認められた。

安全性評価対象 36 例に認められた主な副作用は、AST 増加（36.1%）、ALT 増加（33.3%）、下痢（27.8%）、血中ビリルビン増加（25.0%）、血中アルカリホスファターゼ増加（19.4%）、疲労（19.4%）等であった。（2024 年 11 月 8 日データカットオフ）

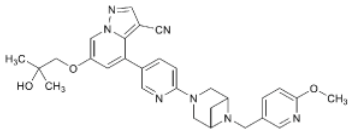
17.3 その他
17.3.1 QT 間隔に対する影響
健康成人 32 例にセルペルカチニブカプセル 320 又は 640mg[注6)] を単回経口投与したとき、QTc 間隔のベースラインからの変化量のプラセボとの差における 90%信頼区間の上限値は、それぞれ 11.87 及び 12.47msec であった[23)]（外国人データ）。［8.2、9.1.1、11.1.2 参照］
注 6）成人に対する本剤の承認用法・用量は 160mg の 1 日 2 回経口投与である。

18. 薬効薬理
18.1 作用機序
セルペルカチニブは、RET、血管内皮増殖因子受容体（VEGFR）、線維芽細胞増殖因子受容体（FGFR）等のキナーゼ活性を阻害する。セルペルカチニブは、RET 融合タンパク等のリン酸化を阻害し、下流のシグナル伝達分子のリン酸化を阻害することにより、腫瘍増殖抑制作用を示すと考えられている[24)]。
18.2 抗腫瘍効果
セルペルカチニブは、*in vitro* において、RET 融合タンパクを発現するヒト非小細胞肺癌由来 LC-2/ad 細胞株及びヒト甲状腺乳頭癌由来 TPC-1 細胞株並びに変異型 RET（C634W 及び M918T）をそれぞれ発現するヒト甲状腺髄様癌由来 TT 及び MZ-CRC1 細胞株

に対して増殖抑制作用を示した。また、セルペルカチニブは、*in vivo* において、LC-2/ad 細胞株、RET 融合タンパクを発現する非小細胞肺癌患者由来 CTG-0838 腫瘍組織片及び TT 細胞株をそれぞれ皮下移植した重症複合型免疫不全-ベージュマウス又はヌードマウスにおいて、腫瘍増殖抑制作用を示した[24)]。

19. 有効成分に関する理化学的知見

一般的名称:セルペルカチニブ (Selpercatinib)〔JAN〕
化　学　名:6-(2-Hydroxy-2-methylpropoxy)-4-(6-{6-[(6-methoxypyridin-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-3-yl}pyridin-3-yl)pyrazolo[1,5-*a*]pyridine-3-carbonitrile
分　子　式:$C_{29}H_{31}N_7O_3$
分　子　量:525.60
性　　状:白色～淡黄色の粉末である。0.1mol/L 塩酸にやや溶けにくく、アセトン及びエタノールに極めて溶けにくく、水にほとんど溶けない。
化学構造式:



融　　点:約 216℃

21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。
〈*RET* 融合遺伝子陽性の進行・再発の甲状腺癌、*RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌〉
21.2 国内での治験症例が極めて限られていることから、製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施することにより、本剤の使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを早期に収集し、本剤の適正使用に必要な措置を講じること。

22. 包装

〈レットヴィモ錠 40mg〉
56 錠 [8 錠 (PTP) ×7]
〈レットヴィモ錠 80mg〉
56 錠 [8 錠 (PTP) ×7]

23. 主要文献

1) 社内資料: セルペルカチニブの毒性試験(2022 年 2 月 25 日承認、CTD2.6.6)
2) 社内資料: セルペルカチニブのがん原性試験
3) 社内資料: 進行癌患者を対象としたセルペルカチニブの第 I/II 相試験(LOXO-RET-17001 試験)(2021 年 9 月 27 日承認、CTD2.7.2.4.2、2.7.6.12、審査報告書)(2022 年 2 月 25 日承認、審査報告書)
4) 社内資料: セルペルカチニブの生物学的同等性試験(J2G-MC-JZJZ 試験)
5) 社内資料: セルペルカチニブの絶対的バイオアベイラビリティ及びマスバランス試験(LOXO-RET-18016 試験)(2021 年 9 月 27 日承認、CTD2.7.6.3)
6) 社内資料: セルペルカチニブの薬物動態に及ぼす食事の影響(J2G-MC-JZPA 試験)
7) 社内資料: セルペルカチニブのヒト血漿蛋白結合率(LOXO-292-DMPK-060 試験)(2021 年 9 月 27 日承認、CTD2.7.2.3.2)
8) 社内資料: セルペルカチニブのヒト血液中/血漿中濃度比(LOXO-292-DMPK-013 試験)(2021 年 9 月 27 日承認、CTD2.7.2.3.3)
9) 社内資料: セルペルカチニブの CYP 代謝(LOXO-292-DMPK-017 試験)(2021 年 9 月 27 日承認、CTD2.7.2.3.5)
10) 社内資料: 様々な重症度の腎機能障害を有する被験者におけるセルペルカチニブの薬物動態(LOXO-RET-18023 試験)(2021 年 9 月 27 日承認、CTD2.7.6.6)
11) 社内資料: 様々な重症度の肝機能障害を有する被験者におけるセルペルカチニブの薬物動態(LOXO-RET-18022 試験)(2021 年 9 月 27 日承認、CTD2.7.6.5)
*12) 社内資料: セルペルカチニブの母集団薬物動態解析及びシミュレーション
13) 社内資料: セルペルカチニブとイトラコナゾール及びリファンピシンの相互作用(LOXO-RET-18014 試験)(2021 年 9 月 27 日承認、CTD2.7.6.7)
14) 社内資料: セルペルカチニブの生理学的薬物動態モデル解析(LOXO-292-DMPK-052 試験)(2021 年 9 月 27 日承認、CTD2.7.2.2.12)
15) 社内資料: セルペルカチニブとミダゾラムの相互作用(LOXO-RET-18017 試験)(2021 年 9 月 27 日承認、CTD2.7.6.8)
16) 社内資料: セルペルカチニブとレパグリニドの相互作用(LOXO-RET-18026 試験)(2021 年 9 月 27 日承認、CTD2.7.6.9)
17) 社内資料: セルペルカチニブの薬物動態に及ぼす食事の影響及びオメプラゾールとの相互作用(LOXO-RET-18015 試験)(2021 年 9 月 27 日承認、CTD2.7.6.2)
18) 社内資料: セルペルカチニブとラニチジン及びオメプラゾールの相互作用(LOXO-RET-19075 試験)(2021 年 9 月 27 日承認、CTD2.7.6.10)
*19) 社内資料: セルペルカチニブとダビガトランの相互作用試験(J2G-MC-JZJV 試験)
*20) 社内資料: セルペルカチニブとロスバスタチンの相互作用試験(J2G-MC-JZPB 試験)
21) 社内資料: セルペルカチニブによるトランスポータ阻害(LOXO-292-DMPK-035 試験)(2021 年 9 月 27 日承認、CTD2.7.2.3.8)
*22) 社内資料: 小児進行がん患者を対象としたセルペルカチニブの第 I/II 相試験(LOXO-RET-18036 試験)
23) 社内資料: セルペルカチニブの QT/QTc 評価(LOXO-RET-18032 試験)(2021 年 9 月 27 日承認、CTD2.7.2.2.8)
24) 社内資料: セルペルカチニブの薬理試験(2021 年 9 月 27 日承認、CTD2.7.6.2)

24. 文献請求先及び問い合わせ先

日本イーライリリー株式会社　医薬情報問合せ窓口
〒651-0086　神戸市中央区磯上通 5 丁目 1 番 28 号
TEL:0120-360-605 (医療関係者向け)
medical.lilly.com/jp

26. 製造販売業者等

26.1 製造販売元

日本イーライリリー株式会社
神戸市中央区磯上通5丁目1番28号

®:登録商標

RET-I002(Rx)

1.8.2 効能・効果（案）及びその設定根拠

1.8.2.1 効能・効果（案）

※本申請に係る変更なし

RET 融合遺伝子陽性の進行・再発の固形腫瘍 *RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌

1.8.2.2 設定根拠

セルペルカチニブは、既承認申請時に提出した LOXO-RET-17001 試験（以下 17001 試験）を主な試験成績として、国内では成人及び 12 歳以上の小児において、以下の効能又は効果で承認を取得している。

- *RET* 融合遺伝子陽性の進行・再発の固形腫瘍
- *RET* 遺伝子変異陽性の根治切除不能な甲状腺髄様癌

今回、小児被験者を対象とした LOXO-RET-18036 試験（以下 18036 試験）にて、*RET* 遺伝子異常を有する小児患者においても良好なベネフィット・リスクプロファイルが示されたことを踏まえ、セルペルカチニブの適応を 2 歳以上の患者に拡大するため、製造販売承認事項一部変更承認申請を行うこととした。

18036 試験において、第 1.8.3.3 項に記載の通り、セルペルカチニブは *RET* 活性化固形腫瘍を有する小児患者における安全性プロファイルに重大な影響を与えることなく、臨床的に意義のあるベネフィットが継続的に示されている。

以上、18036 試験成績より、セルペルカチニブの小児被験者に対する有効性及び安全性が確認できたことから、成人と同様の効能及び効果（案）を設定した。

1.8.3 用法・用量（案）及びその設定根拠

1.8.3.1 用法・用量（案）

通常、成人にはセルペルカチニブとして 1 回 160 mg を 1 日 2 回経口投与する。なお、患者の状態により適宜減量する。
通常、~~1~~2 歳以上の小児には体表面積に合わせて次の投与量（セルペルカチニブとして 1 日量~~回~~約 18~~49~~2 mg/m^2）を ~~1 日 2 回~~経口投与する。なお、患者の状態により適宜減量する。

小児の用量

体表面積	~~1 回~~投与量
0.33 m^2 以上 0.66 m^2 未満	1 回 40 mg　1 日 3 回
0.66 m^2 以上 1.2 m^2 未満	1 回 80 mg　1 日 2 回
1.2 m^2 以上 1.6 m^2 未満	1 回 120 mg　1 日 2 回
1.6 m^2 以上	1 回 160 mg　1 日 2 回

取消線部：削除、下線部：追加

1.8.3.2 用法・用量に関連する注意（案）

7.1 他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。 7.2 本剤投与により副作用が発現した場合には、以下の基準を考慮して、休薬・減量・中止すること。

成人の場合　本剤の減量の目安

減量レベル	投与量
通常投与量	1回 160 mg　1日2回
1段階減量	1回 120 mg　1日2回
2段階減量	1回 80 mg　1日2回
3段階減量	1回 40 mg　1日2回

小児の場合　本剤の減量の目安

体表面積	減量レベル	投与量
0.33 m^2以上 0.66 m^2未満	通常投与量	1回 40 mg　1日3回
	1段階減量	1回 40 mg　1日2回
	2段階減量	1回 40 mg　1日1回
	3段階減量	投与中止
0.66 m^2以上 1.2 m^2未満	通常投与量	1回 80 mg　1日2回
	1段階減量	1回 40 mg　1日2回 ~~1回 40 mg /1回 80 mg 1日2回 (1日量 120 mg)~~
	2段階減量	1回 40 mg　1日 12~~回~~
	3段階減量[注1)]	投与中止 ~~1回 40 mg 1日1回~~
1.2 m^2以上 1.6 m^2未満	通常投与量	1回 120 mg　1日2回
	1段階減量	1回 80 mg　1日2回
	2段階減量	1回 40 mg　1日1回 及び1回 80 mg　1日1回 ~~1回 40 mg /1回 80 mg　1日2回~~ (1日量 120 mg)
	3段階減量[注1)]	1回 40 mg　1日1回
1.6 m^2以上	通常投与量	1回 160 mg　1日2回
	1段階減量	1回 120 mg　1日2回
	2段階減量	1回 80 mg　1日2回
	3段階減量	1回 40 mg　1日2回

注1）過敏症発現時のみ（過敏症以外で2段階減量において忍容性が得られない場合、投与中止）

副作用に対する休薬、減量及び中止基準

副作用	程度[注2)]	処置
ALT又はAST増加	グレード3又は4	グレード1以下に回復するまで休薬し、回復後は2段階減量して投与再開できる。 再開後に2週間以上再発しない場合には、1段階増量することができる。更に4週間以上再発しない場合には、もう1段階増量することができる。 減量した用量で投与中に再発した場合には、中止する。
QT間隔延長	QTc間隔>500msec	QTc間隔<470 msecに回復するまで休薬し、回復後は1段階減量して投与再開できる。 2段階減量した用量で投与中に再発した場合には、中止する。
	重篤な不整脈を疑う所見や症状が認められた場合	中止する。
高血圧	グレード3又は4	回復するまで休薬し、回復後は1段階減量して投与再開できる。
過敏症（アナフィラキシー等の重篤な過敏症を除く）	グレード1～4	回復するまで休薬し、副腎皮質ステロイドの全身投与を考慮する。回復後は副腎皮質ステロイドを併用しながら3段階減量[注3)]して投与再開できる。 再開後に7日以上再発しない場合には、1段階ずつ発現時の用量まで増量できる。増量後に7日以

		上再発しない場合には、副腎皮質ステロイドを漸減する。
間質性肺疾患	グレード 2	回復するまで休薬し、回復後は 1 段階減量して投与再開できる。
	グレード 3 又は 4	中止する。
上記以外の副作用	グレード 3 又は 4	回復するまで休薬し、回復後は 1 段階減量して投与再開できる。

注 2）グレードは NCI-CTCAE ver. 4.03 に準じる。
注 3）体表面積 1.2 ㎡以上の場合のみ

取消線部：削除、下線部：追加

1.8.3.3 設定根拠

18036 試験の第 1 相用量漸増パートでは、92 mg/m^2 BID（bis in die：１日２回）（最大 160 mg BID まで）が RP2D（Recommended Phase 2 dose）として選択された。18036 試験で 92 mg/m^2 BID の開始用量を用いたとき、セルペルカチニブは 2 歳以上の小児被験者に対して下記の通り良好なベネフィット・リスクプロファイルを示した。

18036 試験は、活性化 *RET* 遺伝子異常を有する進行性の固形腫瘍又は中枢神経系原発腫瘍の小児患者を対象とした多施設共同、非盲検、単群、第 1/2 相試験であった。本試験は、第 1 相（用量漸増）パート及び第 2 相（用量拡大）パートから構成された。

第 2 相パートは、RP2D が確定した時点で組入れを開始した。第 2 相パートの主要目的は、IRC（Independent Review Committee）の判定に基づき、腫瘍の種類に応じて RECIST Version 1.1 又は Response Assessment in Neuro-Oncology のいずれか適切な基準を用いて ORR（Objective Response Rate）を評価することであった。

18036 試験では、データカットオフ時点で、*RET* 遺伝子異常を有する進行性の固形腫瘍被験者 36 例が組み入れられ、セルペルカチニブ投与を 1 回以上受けた。Overall Population 36 例のうち、19 例でセルペルカチニブ投与により IRC 評価で奏効が認められた。主な有効性の結果は以下のとおりであった。

- ORR（95% CI）：52.8%（35.5, 69.6）、CR（Complete Response）：10 例、PR（Partial Response）：9 例
- CBR（Clinical Benefit Rate）（95% CI）：77.8%（60.8, 89.9）
- DOR（Duration of Response）の中央値（95% CI）：評価不能（33.4, 評価不能）、データカットオフ時点において、12 ヵ月以上奏効が持続した被験者の割合：84.2%
- DOR の追跡期間の中央値（四分位範囲）：35.06 ヵ月（18.2, 44.2）

がん種に関わらず奏効のほとんどは持続的であり、データカットオフ時点で 25 例（69.4%）が投与継続中であった。ORR の 95%信頼区間の下限値が閾値に設定した 20%を超えており、セルペルカチニブは小児被験者で臨床的に意義のある有効性が確認された。これは、17001 試験での結果ともおおむね一貫していた。

小児被験者に対する安全性プロファイルについて、18036 試験で報告された有害事象は管理可能であり、セルペルカチニブの既知の安全性プロファイルと概ね一貫していた。Overall Population では、主要な毒性は容易に認識可能でほとんどが低グレードであり、セルペルカチニブの用量調整又は通常の臨床治療により管理可能である（第 2.5.5.3 項参照）。また、Overall Population と比較して、日本人集団でも臨床的に重大な新たな安全性の懸念は認められなかった。

大腿骨頭すべり症等の骨端離開はセルペルカチニブ投与を受けた小児患者特有の副作用とされているが、大腿骨骨頭の骨端離開に関連する TEAE（Treatment-Emergent Adverse Event）の発現件数に変更はなく、前回の 18036 試験のデータカットオフ（2023 年 1 月 13 日）以降、新たな報告はなかった。セルペルカチニブは、*RET* 活性化固形腫瘍を有する小児患者における安全性プロファイルに重大な影響を与えることなく、臨床的に意義のあるベネフィットが継続的に示されている。小児集団に特有である大腿骨骨頭の骨端離開を除き、安全性プロファイルは成人集団で認められたものと同様であった。結論として、セルペルカチニブは小児患者を含むすべてのがん種で良好な忍容性を維持していた。

用法用量の設定に際し考慮した事項を以下に示す。

1. 小児患者を対象とした BSA（Body Surface Area）に基づく 92 mg/m^2 BID 相当の投与により、成人患者で良好なベネフィット・リスクが得られている 160 mg BID 投与での曝露量範囲と同程度のセルペルカチニブの曝露量が得られると考えられる。
2. 推奨用量は現在市販されているセルペルカチニブ製剤の最小用量が 40 mg のカプセル又は錠剤であることを考慮し、92 mg/m^2 BID 相当の 1 日投与量に近くなるように設定した。
3. 12 歳未満（低 BSA）の小児に対する用法・用量は米国で既に承認され使用されている用法・用量である。
4. 18036 試験の小児被験者を対象に最終母集団 PK モデルで実施したシミュレーションでは、成人のがん患者にセルペルカチニブ 160 mg BID を投与したときの曝露量と同程度の曝露量が得られるものと考えられる。

以上のことから、用法・用量（案）を設定した。

本剤は各種副作用が認められた場合には休薬、減量等の対応が必要であることから、用法及び用量に関連する注意（案）として 7.2 を設定した。

1.8.4　使用上の注意（案）及びその設定根拠

使用上の注意（案）は、本剤の国際共同臨床試験及びその他試験結果並びに企業中核データシート［Company Core Data Sheet（CCDS）］を参考にして設定した。

使用上の注意（案）	設定根拠
1. 警告 本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。	変更なし
2. 禁忌（次の患者には投与しないこと） 本剤の成分に対しアナフィラキシー等の重篤な過敏症の既往歴のある患者	変更なし
8. 重要な基本的注意 8.1 肝機能障害があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に肝機能検査を行い、患者の状態を十分に観察すること。［11.1.1 参照］	12 歳未満の小児の正常な QTc 間隔を考慮し設定した。
8.2 QT 間隔延長があらわれることがあるので、本剤の投与開始前には患者の QTc 間隔が成人 470msec、12 歳未満の小児 440msec 以下であることを確認するとともに血清電解質検査（カリウム、マグネシウム等）を行うこと。心電図及び血清電解質検査を投与開始後 1 週間時点及び投与開始後 6 ヵ月間は毎月 1 回行い、以降も必要に応じて行うこと。また、必要に応じて電解質補正を行うこと。［11.1.2、17.3.1 参照］	
8.3 高血圧があらわれることがあるので、本剤の投与開始前に血圧が適切に管理されていることを確認すること。本剤投与中は定期的に血圧を測定すること。	
8.4 間質性肺疾患があらわれることがあるので、本剤の投与にあたっては、初期症状（呼吸困難、咳嗽、発熱等）の確認及び胸部画像検査の実施等、患者の状態を十分に観察すること。また、患者に副作用について説明するとともに、間質性肺疾患の初期症状が発現した場合には、速やかに医療機関を受診するよう説明すること。［9.1.3、11.1.5 参照］	
9. 特定の背景を有する患者に関する注意 9.1 合併症・既往歴等のある患者 9.1.1 QT 間隔延長のおそれ又はその既往歴のある患者 QT 間隔延長が発現するおそれがある。先天性/後天性 QT 延長症候群又はその他不整脈の要因になる病態を有する患者には慎重に投与すること。［11.1.2、17.3.1 参照］ 9.1.2 高血圧症の患者 高血圧が悪化するおそれがある。［11.1.4 参照］ 9.1.3 間質性肺疾患のある患者又はその既往歴のある患者 間質性肺疾患が発現又は増悪するおそれがある。［8.4、11.1.5 参照］	変更なし
9.3 肝機能障害患者 9.3.1 重度の肝機能障害のある患者（Child-Pugh 分類 C） 減量を考慮するとともに、患者の状態をより慎重に観察し、副作用の発現に十分注意すること。本剤の血中濃度が上昇し、副作用が増強されるおそれがある。［16.6.2 参照］	変更なし

<table>
<tr><th>使用上の注意（案）</th><th>設定根拠</th></tr>
<tr><td>9.4 生殖能を有する者
9.4.1 妊娠する可能性のある女性には、本剤投与中及び最終投与後 1 ヵ月間において避妊する必要性及び適切な避妊法について説明すること。［9.5 参照］
9.4.2 男性には、本剤投与中及び最終投与後 1 週間においてバリア法（コンドーム）を用いて避妊する必要性について説明すること。［15.2.1 参照］
9.4.3 成長期にある若年男性又は男児に投与する場合には、造精機能の低下があらわれる可能性があることを考慮すること。幼若ラットにおいて、精巣の精上皮変性、精巣上体の精子枯渇、精子運動率低値、異常形態精子比率高値及び受胎能の低下が認められ、精巣及び精巣上体の所見に回復性は認められていない。</td><td>変更なし</td></tr>
<tr><td>9.5 妊婦
妊婦又は妊娠している可能性のある女性には治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。ラットを用いた胚・胎児発生毒性試験において、臨床曝露量（AUC）と同程度の曝露量で胎児死亡及び奇形が認められている。［9.4.1 参照］</td><td>変更なし</td></tr>
<tr><td>9.6 授乳婦
授乳しないことが望ましい。乳汁移行に関するデータはないが、本剤は BCRP の基質であるため、乳汁移行の可能性がある。</td><td>変更なし</td></tr>
<tr><td>9.7 小児等
9.7.1 成長期にある若年者においては、骨成長について以下の点に注意すること。
・骨端線に異常がないか十分に観察すること。骨端線に異常が認められた場合には、投与継続の可否を慎重に判断すること。
・関節痛及び歩行障害について十分に観察すること。大腿骨頭すべり症等の骨端離開があらわれることがある。
［15.2.2 参照］
9.7.2 2 歳未満の小児等を対象とした臨床試験は実施していない。</td><td>2 歳未満の小児等を対象とした臨床試験結果に基づいた用量設定はされていないことから設定した。</td></tr>
<tr><td>10. 相互作用
本剤は、主に CYP3A4 によって代謝され、CYP2C8、CYP3A、P-gp 及び BCRP の阻害作用を示す。また、本剤の溶解度は pH の上昇により低下する。
10.2 併用注意（併用に注意すること）
<table>
<tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr>
<tr><td>CYP2C8 の基質となる薬剤
レパグリニド
ピオグリタゾン
モンテルカスト等
[16.7.6 参照]</td><td>これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。</td><td>本剤が CYP2C8 を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。</td></tr>
<tr><td>CYP3A の基質となる薬剤
ミダゾラム
トリアゾラム
ロミタピド等
[16.7.5 参照]</td><td>これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。</td><td>本剤が CYP3A を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。</td></tr>
<tr><td>CYP3A 阻害剤
イトラコナゾール
クラリスロマイシン
エリスロマイシン等
[16.7.1、16.7.2 参照]</td><td>本剤の副作用が増強されるおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤の減量を考慮す</td><td>これらの薬剤が CYP3A を阻害することにより、本剤の血中濃度が上昇する可能性がある。</td></tr>
</table></td><td>臨床薬理試験の結果及び本剤と併用され得る薬剤を勘案し、本剤のリスクを最小化しベネフィットを保つために適切と考えられる記載を設定した。</td></tr>
</table>

使用上の注意（案）			設定根拠
	るとともに、患者の状態を慎重に観察し、副作用の発現に十分注意すること。		
CYP3A 誘導剤 リファンピシン フェニトイン ボセンタン等 [16.7.3、16.7.4 参照]	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避け、CYP3A 誘導作用のない薬剤への代替を考慮すること。	これらの薬剤等が CYP3A を誘導することにより、本剤の血中濃度が低下する可能性がある。	
セイヨウオトギリソウ(St. John's Wort、セント・ジョーンズ・ワート)含有製品	本剤の有効性が減弱するおそれがあるので、摂取しないよう注意すること。		
プロトンポンプ阻害剤 オメプラゾール ランソプラゾール エソメプラゾール等 [16.7.7 参照]	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤とともに食後に投与すること。	これらの薬剤による胃内 pH の上昇により、本剤の吸収が低下し、本剤の血中濃度が低下する可能性がある。	
H_2受容体拮抗剤 ラニチジン ファモチジン シメチジン等 [16.7.8 参照]	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤と服用時間をずらすこと(ラニチジンを本剤投与 10 時間前及び 2 時間後に投与したときの本剤の血中濃度への影響は限定的であった)。		
制酸剤 炭酸カルシウム 水酸化マグネシウム 水酸化アルミニウム 等	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤と服用時間をずらすこと(制酸剤を本剤投与 2 時間前又は 2 時間後に投与したときの本剤の血中濃度への影響は限定的であった)。		
治療域の狭い P-gp の基質となる薬剤 ジゴキシン シロリムス エベロリムス等 [16.7.9 参照]	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤が P-gp を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。	
BCRP の基質となる薬剤 ロスバスタチン メトトレキサート イマチニブ等 [16.7.10 参照]		本剤が BCRP を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。	
11. 副作用 次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。 11.1.1 肝機能障害（37.8%） ［8.1 参照］ 11.1.2 QT 間隔延長（13.9%） ［8.2、9.1.1、17.3.1 参照］ 11.1.3 過敏症（4.9%） 発疹、発熱等の症状を伴う遅発性の過敏症があらわれることがある。［7.2 参照］ 11.1.4 高血圧（28.0%） ［9.1.2 参照］ 11.1.5 間質性肺疾患（0.6%） ［8.4、9.1.3 参照］			本剤の副作用として臨床試験の結果から本剤投与との間に関連性があると判断された事象を CCDS の記載を参考に設定した。なお、事象の頻度は LIBRETTO-001 試験の第 II 相パートに組み入れられた NSCLC 及び甲状腺癌患者、LIBRETTO-001 試験の第 I 相パート及び第 II 相パートに組み入れられ開始用量として本剤 160mg を 1 日 2 回投与された NSCLC 及び甲状腺癌以外の固形腫瘍患者（Tissue-Agnostic Safety Population）並びに LIBRETTO-121 試験の第 I 相パート及び第 II 相パートに組み入れられ開始用量として開始用量として 92mg/m^2 を 1 日 2 回投与された小児進行がん患者における頻度に基づき算出した。

<table>
<tr><th>使用上の注意（案）</th><th>設定根拠</th></tr>
<tr><td>11.2 その他の副作用
<table>
<tr><th>副作用分類</th><th>20%以上</th><th>5～20%未満</th><th>5%未満</th><th>頻度不明</th></tr>
<tr><td>消化器</td><td>口内乾燥(31.9%)、下痢</td><td>便秘、悪心、口内炎、腹痛</td><td>嘔吐</td><td></td></tr>
<tr><td>一般・全身及び投与部位反応</td><td>疲労</td><td>浮腫</td><td>発熱</td><td></td></tr>
<tr><td>呼吸器</td><td></td><td></td><td>鼻出血、肺炎</td><td></td></tr>
<tr><td>感染症</td><td></td><td></td><td>尿路感染</td><td></td></tr>
<tr><td>内分泌</td><td></td><td></td><td>甲状腺機能低下症</td><td></td></tr>
<tr><td>代謝・栄養障害</td><td></td><td>食欲減退</td><td></td><td></td></tr>
<tr><td>精神神経系</td><td></td><td>頭痛</td><td>浮動性めまい</td><td></td></tr>
<tr><td>皮膚</td><td></td><td>発疹</td><td></td><td></td></tr>
<tr><td>生殖器</td><td></td><td>勃起不全</td><td></td><td></td></tr>
<tr><td>血液</td><td></td><td>血小板減少、白血球減少、好中球減少</td><td>リンパ球減少、貧血</td><td></td></tr>
<tr><td>臨床検査値異常</td><td></td><td>血中クレアチニン増加</td><td>低マグネシウム血症、低アルブミン血症、低カリウム血症、低カルシウム血症</td><td></td></tr>
<tr><td>その他</td><td></td><td></td><td>乳び腹水</td><td>乳び胸</td></tr>
</table></td><td></td></tr>
<tr><td>14. 適用上の注意
14.1 薬剤交付時の注意
PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。PTP シートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。</td><td>変更なし</td></tr>
<tr><td>15. その他の注意
15.2 非臨床試験に基づく情報
15.2.1 セルペルカチニブは、ラット小核試験において、臨床用量 160mg1 日 2 回で得られる C_{max} の 5.2 倍に相当する用量で遺伝毒性が陽性であった。［9.4.2 参照］
15.2.2 動物試験（成長板が閉鎖していない幼若ラット、若齢ラット及び若齢ミニブタ）において、本剤の反復投与により骨端成長板の異常（骨端軟骨の肥大、過形成及び異形成）が、ヒトに 160mg1 日 2 回の用量で投与したときの臨床曝露量よりも低い曝露量で認められている。また、幼若ラットにおいて、骨端成長板の変化に関連して、骨密度及び大腿骨長の低値が、ヒトに 160mg1 日 2 回の用量で投与したときの臨床曝露量のそれぞれ 0.8 倍及び 1.9 倍で認められている。［9.7.1 参照］
15.2.3 ラットを用いた 2 年間がん原性試験において、ヒトに 160mg1 日 2 回の用量で投与したときの臨床曝露量に相当する用量で雌に腟腫瘍が認められている。</td><td>変更なし</td></tr>
</table>

レットヴィモカプセル 40mg
レットヴィモカプセル 80mg
レットヴィモ錠 40mg
レットヴィモ錠 80mg

1.9　一般的名称に係る文書

日本イーライリリー株式会社

薬生薬審発 0310 第１号
令 和 ２ 年 ３ 月 １０ 日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬・生活衛生局医薬品審査管理課長
（　　公　　印　　省　　略　　）

医薬品の一般的名称について

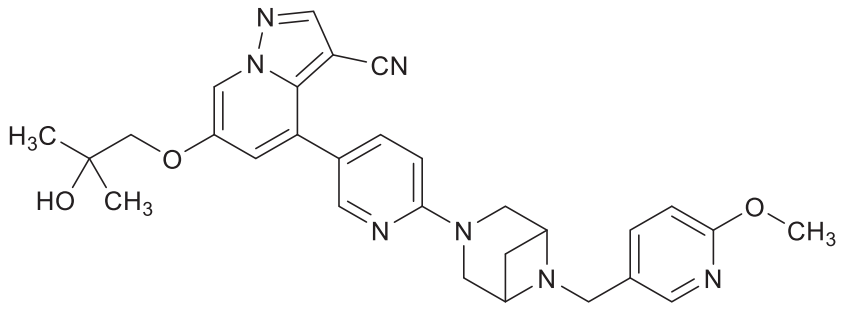
標記については、「医薬品の一般的名称の取扱いについて（平成 18 年３月 31 日薬食発第 0331001 号厚生労働省医薬食品局長通知）」等により取り扱っているところです。今般、我が国における医薬品の一般的名称（以下「JAN」という。）について、新たに別添のとおり定めたので、御了知の上、貴管下関係業者に周知方よろしく御配慮願います。

（参照）
「日本医薬品一般的名称データベース」https://jpdb.nihs.go.jp/jan/Default.aspx
（別添の情報のうち、JAN 以外の最新の情報は、当該データベースの情報で対応することとしています。なお、本年２月末より当該 URL を変更しており、令和２年４月初頭以降は従前 URL でのアクセスは不可となります。）

登録番号　301-4-B4

JAN（日本名）：セルペルカチニブ

JAN（英　名）：Selpercatinib



$C_{29}H_{31}N_7O_3$

6-(2-ヒドロキシ-2-メチルプロポキシ)-4-(6-{6-[(6-メトキシピリジン-3-イル)メチル]-3,6-ジアザビシクロ[3.1.1]ヘプタン-3-イル}ピリジン-3-イル)ピラゾロ[1,5-*a*]ピリジン-3-カルボニトリル

6-(2-Hydroxy-2-methylpropoxy)-4-(6-{6-[(6-methoxypyridin-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-3-yl}pyridin-3-yl)pyrazolo[1,5-*a*]pyridine-3-carbonitrile

WHO Drug Information, Vol. 33, No. 3, 2019

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names: List 82

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [*Off. Rec. Wld Health Org.*, 1955, **60**, 3 (Resolution EB15.R7); 1969, **173**, 10 (Resolution EB43.R9); Resolution EB115.R4 (EB115/2005/REC/1)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.
Lists of Proposed (1–1117) and Recommended (1–78) International Nonproprietary Names can be found in *Cumulative List No. 17, 2017* (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES: Liste 82

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [*Actes off. Org. mond. Santé*, 1955, **60**, 3 (résolution EB15.R7); 1969, **173**, 10 (résolution EB43.R9); résolution EB115.R4 (EB115/2005/REC/1)] les dénominations ci-dessous sont choisies par l'Organisation mondiale de la Santé en tant que dénominations communes internationales recommandées. L'inclusion d'une dénomination dans les listes de DCI recommandées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.
On trouvera d'autres listes de Dénominations communes internationales proposées (1–117) et recommandées (1–78) dans la *Liste récapitulative No. 17, 2017* (disponible sur CD-ROM seulement).

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS: Lista 82

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [*Act. Of. Mund. Salud*, 1955, **60**, 3 (Resolución EB15.R7); 1969, **173**, 10 (Resolución EB43.R9); Résolution EB115.R4 (EB115/2005/REC/1) EB115.R4 (EB115/2005/REC/1)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.
Las listas de Denominaciones Comunes Internacionales Propuestas (1–117) y Recomendadas (1–78) se encuentran reunidas en *Cumulative List No. 17, 2017* (disponible sólo en CD-ROM).

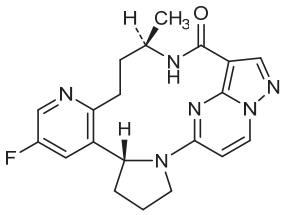
selitrectinibum

selitrectinib — (2^2R,6*R*)-3^5-fluoro-6-methyl-1(5,3)-pyrazolo[1,5-*a*]pyrimidina-3(3,2)-pyridina-2(1,2)-pyrrolidinacyclooctaphan-8-one

sélitrectinib — (2^2R,6*R*)-3^5-fluoro-6-méthyl-1(5,3)-pyrazolo[1,5-*a*]pyrimidina-3(3,2)-pyridina-2(1,2)-pyrrolidinacyclooctaphan-8-one

selitrectinib — (2^2R,6*R*)-3^5-fluoro-6-metil-1(5,3)-pirazolo[1,5-*a*]pirimidina-3(3,2)-piridina-2(1,2)-pirrolidinaciclooctafan-8-ona

$C_{20}H_{21}FN_6O$



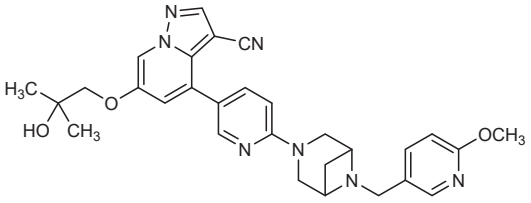
selpercatinibum

selpercatinib — 6-(2-hydroxy-2-methylpropoxy)-4-(6-{6-[(6-methoxypyridin-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-3-yl}pyridin-3-yl)pyrazolo[1,5-*a*]pyridine-3-carbonitrile

selpercatinib — 6-(2-hydroxy-2-méthylpropoxy)-4-(6-{6-[(6-méthoxypyridin-3-yl)méthyl]-3,6-diazabicyclo[3.1.1]heptan-3-yl}pyridin-3-yl)pyrazolo[1,5-*a*]pyridine-3-carbonitrile

selpercatinib — 6-(2-hidroxi-2-metilpropoxi)-4-(6-{6-[(6-metoxipiridin-3-il)metil]-3,6-diazabiciclo[3.1.1]heptan-3-il}piridin-3-il)pirazolo[1,5-*a*]piridina-3-carbonitrilo

$C_{29}H_{31}N_7O_3$



semorinemabum #

semorinemab — immunoglobulin G4-kappa, anti-[*Homo sapiens* MAPT (microtubule-associated protein tau, tau)], monoclonal antibody;

レットヴィモカプセル 40mg
レットヴィモカプセル 80mg
レットヴィモ錠 40mg
レットヴィモ錠 80mg

1.10　毒薬・劇薬等の指定審査資料のまとめ

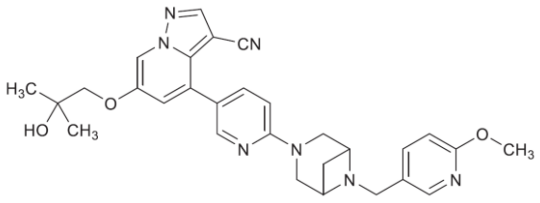
日本イーライリリー株式会社

目次

1.10　毒薬・劇薬等の指定審査資料のまとめ 1

1.10 毒薬・劇薬等の指定審査資料のまとめ

表 1.10-1 毒薬・劇薬等の指定審査資料のまとめ（現行）

<table>
<tr><td>化学名・別名</td><td>化学名: 6-(2-Hydroxy-2-methylpropoxy)-4-(6-{6-[(6-methoxypyridin-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-3-yl}pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile
（別名: セルペルカチニブ及びその製剤）</td></tr>
<tr><td>構造式</td><td></td></tr>
<tr><td>効能・効果</td><td>RET 融合遺伝子陽性の進行・再発の固形腫瘍
RET 遺伝子変異陽性の根治切除不能な甲状腺髄様癌</td></tr>
<tr><td>用法・用量</td><td>通常、成人にはセルペルカチニブとして 1 回 160 mg を 1 日 2 回経口投与する。なお、患者の状態により適宜減量する。
通常、12 歳以上の小児には体表面積に合わせて次の投与量（セルペルカチニブとして 1 回約 92 mg/m^2）を 1 日 2 回経口投与する。なお、患者の状態により適宜減量する。

小児の用量
<table>
<tr><th>体表面積</th><th>1 回投与量</th></tr>
<tr><td>1.2 m^2 未満</td><td>80 mg</td></tr>
<tr><td>1.2 m^2 以上 1.6m^2 未満</td><td>120 mg</td></tr>
<tr><td>1.6 m^2 以上</td><td>160 mg</td></tr>
</table></td></tr>
<tr><td>劇薬等の指定</td><td>原薬及び製剤：劇薬
処方箋医薬品</td></tr>
<tr><td>市販名及び有効成分・分量</td><td>原体：セルペルカチニブ
製剤：
レットヴィモカプセル 40mg（1 カプセル中 40 mg 含有）
レットヴィモカプセル 80mg（1 カプセル中 80 mg 含有）
レットヴィモ錠 40mg（1 錠中 40 mg 含有）
レットヴィモ錠 80mg（1 錠中 80 mg 含有）</td></tr>
<tr><td>毒性</td><td>単回投与毒性（経口）
<table>
<tr><th>動物種</th><th>概略の致死量 (mg/kg)</th></tr>
<tr><td>ラット</td><td>＞2000[a]</td></tr>
<tr><td>ミニブタ</td><td>＞65[b]</td></tr>
</table>
a：ラット小核予備試験（単回投与）の成績から推定した。
b：ミニブタ 14 日間投与毒性試験の初回投与後の成績から推定した。

反復投与毒性（経口）
<table>
<tr><th>動物種
期間</th><th>用量
(mg/kg)</th><th>NOAEL
(mg/kg)</th><th>主な毒性所見</th></tr>
</table></td></tr>
</table>

	ラット 28 日間	雄：5, 20, 75/45[a] 雌：15, 50, 150/120[b]	雄：20 雌：50	死亡又は切迫屠殺：75/45（雄 2 例）、150/120（雌 1 例） 75/45（雄）、150/120（雌）：円背位、立毛、削痩（雄）、斜視（雌）、透明口腔内分泌物（雌）、被毛の汚れ（雌）、不正咬合及び白色切歯、粗毛（雌）、体重↓（雄）、体重増加量↓、摂餌量↓、総白血球数↑（雌）、好中球数↑（雌）、単球数↑（雌）、大型非染色細胞数↑（雌）、A/G 比↓（雌）、総タンパク↓、アルブミン↓、Ca↓、AST↑、γ-GTP↑、グルコース↓（雄）、尿素窒素↑（雌）、肝臓重量↓（雄）、胸腺重量↓（雄）、骨端軟骨異形成、骨髄細胞数減少、組織鉱質沈着、膵腺房細胞の変性／壊死（雄） 以下、非毒性的変化： 75/45（雄）、150/120（雌）：ブルンナー腺の陰窩／導管拡張（雄）、舌の上皮萎縮、肺胞マクロファージの増加、膵腺房細胞の変性／壊死（雌） ≧20（雄）：網状赤血球数↓、平均赤血球容積↑、平均赤血球ヘモグロビン↑、ALT↑、ALP↑、コレステロール↑、無機リン↑、ヘモグロビン↑、ヘマトクリット↑ 20（雄）：骨端軟骨異形成、膵腺房細胞の変性／壊死 ≧5（雄）：血小板数↓ ≧50（雌）：平均赤血球容積↑、平均赤血球ヘモグロビン↑、ALT↑、ALP↑、無機リン↑、ヘモグロビン↑、ヘマトクリット↑
	ラット 91 日間	雄：2, 7.5, 20 雌：7.5, 25, 75	雄：7.5 雌：25	死亡又は切迫屠殺：2（雄 1 例）、25（雌 1 例）、いずれもセルペルカチニブ投与と関連しない 20（雄）、75（雌）：切歯の異常（不正咬合、白色切歯及び切歯喪失）、被毛菲薄化、骨髄細胞数減少、精巣の小型化又は軟化、精巣重量↓、精細管変性／萎縮、精巣上体の管腔内細胞残屑・管腔内精子↓、精巣上体重量↓、膣上皮の粘液分泌↑、性周期の変化（判定不能） 以下、非毒性的変化： 20（雄）、75（雌）：肺胞マクロファージ浸潤、総タンパク↓（雌）、A/G 比↓（雌）、無機リン↑、尿 pH↑、ヘモグロビン↑（雄）、ヘマトクリット↑（雄）、平均赤血球容積↑（雄）、平均赤血球ヘモグロビン↑（雄） ≧7.5（雄）：網状赤血球数↓ 7.5（雄）：精細管変性／萎縮 ≧25（雌）：膣上皮の粘液分泌↑及び性周期判定不能（1 例）、平均赤血球容積↑、平均赤血球ヘモグロビン↑、アルブミン↓ ≧7.5（雌）：ヘモグロビン又はヘマトクリット↑
	ミニブタ 28 日間	2, 5, 12	12	死亡又は切迫屠殺：なし 以下、非毒性的変化： 12：尿素窒素↑（雌）、ALP↑、カリウム↑、無機リン↑ ≧5：赤血球量↑、下顎リンパ節及び腸間膜リンパ節のリンパ球低細胞性 ≧2：舌及び前胃の上皮萎縮

	ミニブタ 91 日間	2, 5, 15[c]	雄：＜2 雌：5	死亡又は切迫屠殺：15（雄 3 例、雌 4 例）、2（雌 1 例：セルペルカチニブ投与と関連しない） 15：跛行、起立不同意、横臥位、疼痛、赤色口腔内分泌物、活動性低下、食欲不振、前胃粘膜上皮の萎縮、変性／壊死、びらん／潰瘍及び／又は好中球性炎症、大腿骨の骨端軟骨の肥厚（骨端軟骨異形成）、卵巣の黄体減少及び黄体嚢胞、食道の粘膜萎縮、粘膜変性／壊死、好中球性炎症及び／又は潰瘍／びらん）、舌の粘膜萎縮、ALP↑、無機リン↑、尿素窒素↑、Na↑、尿検査値の変化（尿比重↑、尿タンパク↑） ≧2：精細管変性／萎縮、精巣上体の管腔内細胞残屑、精巣重量↓、精巣上体重量↓ 以下、非毒性的変化： 5：QTc（雌）↑ 2 及び 5：黄体嚢胞

略語：↑＝増加、↓＝減少、A/G 比＝アルブミン：グロブリン比、ALP＝アルカリフォスファターゼ、ALT＝アラニンアミノトランスフェラーゼ、AST＝アスパラギン酸アミノトランスフェラーゼ、Ca＝カルシウム、Na＝ナトリウム、γ-GTP＝γ-グルタミルトランスフェラーゼ活性、QTc＝心拍数で補正した QT

a. 75 mg/kg の用量で投与を開始したが、Day 8～10 に休薬した後、Day 11 に 45 mg/kg に減量した。
b. 150 mg/kg の用量で投与を開始したが、Day 16 に 120 mg/kg に減量し、Day 18～20 に休薬した後、Day 21 に 120 mg/kg で投与を再開した。
c. Day 27 に雄 3 例、Day 26 に雌 4 例をそれぞれ瀕死屠殺した。同群の残りの動物についてはこの時点で投与を終了し、4 週間の回復期間の後剖検した。

副作用

国際共同第 1/2 相試験（LOXO-RET-17001 試験）
対象：
RET 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌
RET 融合遺伝子陽性の根治切除不能な甲状腺癌
RET 遺伝子変異陽性の根治切除不能な甲状腺髄様癌

副作用発現率 566/653 例 (86.7%)　臨床検査値異常発現率 342/653 例 (52.4%)

副作用の種類	件数／評価例数（発現割合）	臨床検査値異常の種類	件数／評価例数（発現割合）
口内乾燥	234/653 (35.8%)	ALT 増加	184/653 (28.2%)
ALT 増加	184/653 (28.2%)	AST 増加	177/653 (27.1%)
AST 増加	177/653 (27.1%)	心電図 QT 延長	97/653 (14.9%)
高血圧	175/653 (26.8%)	血中クレアチニン増加	81/653 (12.4%)
下痢	147/653 (22.5%)	血中 ALP 増加	51/653 (7.8%)

国際共同第 1/2 相試験（LOXO-RET-17001 試験）
対象：*RET* 融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）

副作用発現率 50/55 例 (90.9%)　臨床検査値異常発現率

副作用の種類	件数／評価例数（発現割合）	臨床検査値異常の種類	件数／評価例数（発現割合）
ALT 増加	19/55 (34.5%)	AST 増加	36/54 (66.7%)
AST 増加	15/55 (27.3%)	ALT 増加	31/54 (57.4%)
口内乾燥	15/55 (27.3%)	血中 ALP 増加	26/54 (48.1%)
下痢	10/55 (18.2%)	血中アルブミン減少	26/54 (48.1%)
高血圧	9/55 (16.4%)	血中ナトリウム減少	26/54 (48.1%)

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製剤：輸入

表 1.10-2 毒薬・劇薬等の指定審査資料のまとめ（変更）

<table>
<tr><td>化学名・別名</td><td></td></tr>
<tr><td>構造式</td><td></td></tr>
<tr><td>効能・効果</td><td></td></tr>
<tr><td>用法・用量</td><td>通常、成人にはセルペルカチニブとして 1 回 160 mg を 1 日 2 回経口投与する。なお、患者の状態により適宜減量する。
通常、~~1~~2 歳以上の小児には体表面積に合わせて次の投与量（セルペルカチニブとして ~~1 回約 92 mg/m²~~1 日量約 184 mg/m²）を ~~1 日 2 回~~経口投与する。なお、患者の状態により適宜減量する。
小児の用量
<table>
<tr><th>体表面積</th><th>~~1 回~~投与量</th></tr>
<tr><td>0.33 m² 以上 0.66 m² 未満</td><td>1 回 40 mg　1 日 3 回</td></tr>
<tr><td>0.66 m² 以上 1.2 m² 未満</td><td>1 回 80 mg　1 日 2 回</td></tr>
<tr><td>1.2 m² 以上 1.6 m² 未満</td><td>1 回 120 mg　1 日 2 回</td></tr>
<tr><td>1.6 m² 以上</td><td>1 回 160 mg　1 日 2 回</td></tr>
</table>
下線部：追加　取消線部：削除</td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td></td></tr>
<tr><td>毒性</td><td></td></tr>
<tr><td>副作用</td><td>国際共同第 1/2 相試験（LOXO-RET-17001 試験）
対象：
RET 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌
RET 融合遺伝子陽性の根治切除不能な甲状腺癌
RET 遺伝子変異陽性の根治切除不能な甲状腺髄様癌

副作用発現率 566/653 例 (86.7%)　臨床検査値異常発現率 342/653 例 (52.4%)
<table>
<tr><th>副作用の種類</th><th>件数／評価例数（発現割合）</th><th>臨床検査値異常の種類</th><th>件数／評価例数（発現割合）</th></tr>
<tr><td>口内乾燥</td><td>234/653 (35.8%)</td><td>ALT 増加</td><td>184/653 (28.2%)</td></tr>
<tr><td>ALT 増加</td><td>184/653 (28.2%)</td><td>AST 増加</td><td>177/653 (27.1%)</td></tr>
<tr><td>AST 増加</td><td>177/653 (27.1%)</td><td>心電図 QT 延長</td><td>97/653 (14.9%)</td></tr>
<tr><td>高血圧</td><td>175/653 (26.8%)</td><td>血中クレアチニン増加</td><td>81/653 (12.4%)</td></tr>
<tr><td>下痢</td><td>147/653 (22.5%)</td><td>血中 ALP 増加</td><td>51/653 (7.8%)</td></tr>
</table>

国際共同第 1/2 相試験（LOXO-RET-17001 試験）
対象：*RET* 融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）
副作用発現率 50/55 例 (90.9%)　臨床検査値異常発現率
<table>
<tr><th>副作用の種類</th><th>件数／評価例数（発現割合）</th><th>臨床検査値異常の種類</th><th>件数／評価例数（発現割合）</th></tr>
<tr><td>ALT 増加</td><td>19/55 (34.5%)</td><td>AST 増加</td><td>36/54 (66.7%)</td></tr>
</table></td></tr>
</table>

	AST 増加 15/55 (27.3%)　ALT 増加 31/54 (57.4%) 口内乾燥 15/55 (27.3%)　血中 ALP 増加 26/54 (48.1%) 下痢 10/55 (18.2%)　血中アルブミン減少 26/54 (48.1%) 高血圧 9/55 (16.4%)　血中ナトリウム減少 26/54 (48.1%) 国際共同第 1/2 相試験（LOXO-RET-18036 試験） 対象：*RET* 遺伝子異常を有する進行固形腫瘍又は中枢神経系原発腫瘍の小児被験者 副作用発現率 33/36 例 (91.7%)　臨床検査値異常発現率 副作用の種類 / 件数／評価例数（発現割合） AST 増加 13/36 (36.1%) ALT 増加 12/36 (33.3%) 下痢 10/36 (27.8%) 血中ビリルビン増加 8/36 (22.2%) 血中 ALP 増加 7/36 (19.4%) 疲労 7/36 (19.4%) 高リン血症 7/36 (19.4%) 臨床検査値異常の種類 / 件数／評価例数（発現割合） カルシウム減少 22/36 (61.1%) ALT 増加 21/36 (58.3%) アルブミン減少 19/36 (52.8%) ALP 増加 18/36 (50.0%) AST 増加 18/36 (50.0%) 下線部：追加
会社	

レットヴィモカプセル 40mg
レットヴィモカプセル 80mg
レットヴィモ錠 40mg
レットヴィモ錠 80mg

1.12　添付資料一覧

日本イーライリリー株式会社

1.12 添付資料一覧

第5部（モジュール5）：臨床試験報告書
5.2 全臨床試験一覧表

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.2	全臨床試験一覧表	－	－	－	－	－	－	－

5.3 臨床試験報告書
5.3.1 生物薬剤学試験報告書
5.3.1.1 バイオアベイラビリティ（BA）試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.1.1.1	該当なし							

5.3.1.2 比較BA試験及び生物学的同等性（BE）試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.1.2.1	治験総括報告書J2G-MC-JZJU試験: An Open-Label, Randomized Study to Evaluate the Relative Bioavailability of Selpercatinib in 3 Formulations for Pediatric Use	-	2021年12月～2022年3月	米国	国外	－	参考資料	無

5.3.1.3 In Vitro-In Vivoの関連を検討した試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.1.3.1	該当なし							

5.3.1.4 生物学的及び理化学的分析法検討報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.1.4.1	該当なし							

5.3.2 ヒト生体試料を用いた薬物動態関連の試験報告書
5.3.2.1 血漿蛋白結合試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.2.1.1	該当なし							

5.3.2.2 肝代謝及び薬物相互作用試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.2.2.1	該当なし							

5.3.2.3 他のヒト生体試料を用いた試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.2.3.1	該当なし							

5.3.3 臨床薬物動態（PK）試験報告書
5.3.3.1 健康被験者におけるPK及び初期忍容性試験報告

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.3.1.1	該当なし							

5.3.3.2 患者におけるPK及び初期忍容性試験報告書

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.3.2.1	該当なし							

5.3.3.3 内因性要因を検討したPK試験報告書

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.3.3.1	該当なし							

5.3.3.4 外因性要因を検討したPK試験報告書

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.3.4.1	治験総括報告書J2G-MC-JZJV試験: An Open-Label Study to Investigate the Effect of Selpercatinib on the Pharmacokinetics of Dabigatran in Healthy Volunteers	-	2021年3月～2021年5月	米国	国外	-	参考資料	有
5.3.3.4.2	治験総括報告書J2G-MC-JZPB試験: A Phase 1, Open-Label, Drug Interaction Study to Investigate the Effect of Single Dose Selpercatinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants	-	2023年7月～2023年10月	米国	国外	-	参考資料	有

5.3.3.5 ポピュレーションPK試験報告書

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.3.5.1	Population PK Modelling and Simulation to Support Posology in Paediatrics and Adolescents	-	(20[redacted]年[redacted]月)	-	国外	-	参考資料	有
5.3.3.5.2	Population PK modelling and simulation to support posology in pediatrics - Simulations for Japanese pediatric and adolescent patients (2 to <18 years)	-	(20[redacted]年[redacted]月)	-	国外	-	参考資料	有

5.3.4 臨床薬力学(PD)試験報告書

5.3.4.1 健康被験者におけるPD試験及びPK/PD試験報告書

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.4.1.1	該当なし							

5.3.4.2 患者におけるPD試験及びPK/PD試験報告書

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.4.2.1	該当なし							

5.3.5 有効性及び安全性試験報告書

5.3.5.1 申請する適応症に関する比較対照試験報告書

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.5.1.1	該当なし							

5.3.5.2 非対照試験報告書

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.5.2.1	治験総括報告書LOXO-RET-18036試験: A Phase 1/2 Study of the Oral *RET* Inhibitor LOXO 292 in Pediatric Patients with Advanced *RET*-Altered Solid or Primary Central Nervous System Tumors	-	2019年6月～実施中	日本、米国、他	国内外	-	評価資料	有

5.3.5.3 複数の試験成績を併せて解析した報告書

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.5.3.1	該当なし							

5.3.5.4 その他の試験報告書

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.5.4.1	該当なし							

5.3.6 市販後の使用経験に関する報告書

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.6.1	PERIODIC SAFETY UPDATE REPORT (PSUR) in the Format of ICH E2C (R2)	-	20[redacted]年[redacted]月～20[redacted]年[redacted]月 (20[redacted]年[redacted]月)	-	国外	-	参考資料	無
5.3.6.2	新医療用医薬品に関する安全性定期報告書	-	20[redacted]年[redacted]月～20[redacted]年[redacted]月 (20[redacted]年[redacted]月)	-	国内	-	参考資料	無

5.3.7 患者データ一覧表及び症例記録

5.3.7.1 症例一覧表

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.7.1.1	該当なし	-	-	-				

5.3.7.2 有害事象発現症例一覧表

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.7.2.1	有害事象発現症例一覧表 LOXO-RET-18036試験	-	-	-	国内外	-	評価資料	有

5.3.7.3 重篤な有害事象発現症例一覧表

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.7.3.1	重篤な有害事象発現症例一覧表 LOXO-RET-18036試験	-	-	-	国内外	-	評価資料	有

5.3.7.4 臨床検査値異常症例一覧表

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.7.4.1	臨床検査値異常症例一覧表 LOXO-RET-18036試験	−	−	−	国内外	−	評価資料	有

5.3.7.5 臨床検査値変動図

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.7.5.1	該当なし	−	−	−				

5.4 参考文献

添付資料番号	タイトル	著者	試験実施期間(報告書承認年月)	試験実施場所	報種類(国内、国外)	掲載誌	参考文献	申請電子データの提出有無
モジュール2.5で引用した文献を添付した。								

提出すべき資料がない項目リスト

[redacted]