Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Retevmo

Active ingredient/s: Selpercatinib

Sponsor: Eli Lilly Australia Pty Ltd

January 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AUC	Area under concentration time curve
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
DLP	Data lock point
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FDA	Food and Drug Administration (United States)
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PI	Product Information
PK	Pharmacokinetic(s)
PSUR	Periodic safety update report
RECIST	The Response Evaluation Criteria In Solid Tumours
RET	Rearranged during transfection
RMP	Risk management plan
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
TGO91	Therapeutic Goods Order 91
T_{max}	Time to maximum concentration
USA	United States (of America)
Vd	Volume of distribution

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Retevmo
Active ingredient:	Selpercatinib
Decision:	Approved for provisional registration
Date of decision:	27 June 2023
Date of entry onto ARTG:	3 July 2023
ARTG numbers:	391330 and 391331
, *Black Triangle Scheme*	Yes
for the current submission:	As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration
Sponsor's name and address:	Eli Lilly Australia Pty Ltd Level 9, 60 Margaret Street, Sydney, NSW 2000
Dose form:	Immediate release hard capsule
Strengths:	40 mg and 80 mg
Container:	Blister pack
Pack sizes:	40 mg - 14, 56, 42, 168 capsules 80 mg – 14, 28, 56, and 112 capsules
Approved therapeutic use for the current submission:	*Retevmo has provisional approval for the treatment of adult patients with locally advanced or metastatic RET fusion positive non-small cell lung cancer (NSCLC).* *The decision to approve this indication has been made on the basis of objective response rate (ORR) and duration of response (DOR) from a single arm study. Continued approval of this indication depends on verification and description of benefit in a confirmatory trial.*
Route of administration:	Oral
Dosage:	The recommended dose of Retevmo based on body weight is: • Less than 50 kg: 120 mg twice daily. • 50 kg or greater: 160 mg twice daily. If a patient vomits or misses a dose, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken. Treatment should be continued until disease progression or unacceptable toxicity.

	For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D
	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
	The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Eli Lilly Australia Pty Ltd (the sponsor) to register Retevmo (selpercatinib) 40 mg, 80 mg, immediate released hard capsule, blister pack for the following proposed indication:[1]

> *The treatment of adult patients with advanced or metastatic RET fusion positive non-small cell lung cancer (NSCLC).*

Non small-cell lung cancer (NSCLC) is the most common form of lung cancer and often presents with locally advanced and/or metastatic disease that is not curable. The choice of systemic palliative therapy is complex because tumours can express a range of known genetic mutations that promote cancer growth. If a cancer expresses one or more of these 'drivers', such as mutations of *EGFR, ALK, ROS1, BRAF, MET*, or *RET* genes, then targeted therapy can be selected. Tumours without driver mutations are usually initially treated with platinum-based chemotherapy plus a checkpoint inhibitor (for example, pembrolizumab).

Selpercatinib is a targeted therapy that acts against mutated *RET*, a tyrosine kinase that drives cell division. The *RET* gene can be altered in a number of ways in lung cancers, including point mutations or chromosomal rearrangements (fusions). It is an uncommon driver mutation in NSCLC, being present in 1 to 2% of cancers, and is associated with adenocarcinomas of female non-smokers younger than the average NSLC patient.

This evaluation was facilitated through Project Orbis, an initiative of the United States Food and Drug Administration (FDA) Oncology Center of Excellence. Under this project, the FDA, Health Canada, Swissmedic and the TGA collaboratively reviewed the submission. This evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

Regulatory status

This product is considered a new chemical entity medicine for Australian regulatory purposes.

At the time the TGA considered this submission, a similar submission had been approved in United States of America (USA) on 21 September 2022, European Union (EU) on 21 June 2022. United Kingdom on 26 October 2022, and Canada on 15 June 2021.

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Status	Approved indications
United States of America	Approved on 21 September 2022	*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.*
European Union	Approved on 21 June 2022	*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*
United Kingdom	Approved on 26 October 2022	*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*
Canada	Approved on 15 June 2021	*Retevmo (selpercatinib) is indicated as monotherapy for the treatment of: metastatic RET fusion-positive non-small cell lung cancer (NSCLC) in adult patients.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the provisional registration process.

Table 2: Timeline for Submission PM-2022-02343-1-4

Description	Date
Determination (Provisional)	28 March 2022
Submission dossier accepted and first round evaluation commenced	1 August 2022
First round evaluation completed	13 January 2023
Sponsor provides responses on questions raised in first round evaluation	21 February 2023
Second round evaluation completed	31 March 2023
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	21 April 2023
Sponsor's pre-Advisory Committee response	12 May 2023
Advisory Committee meeting	1 and 2 June 2023
Registration decision (Outcome)	27 June 2023
Completion of administrative activities and registration on ARTG	3 July 2023
Number of working days from submission dossier acceptance to registration decision*	181

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

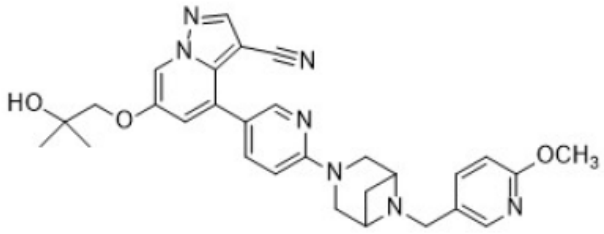
This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

Retevmo is a small molecule inhibitor of the *RET* receptor tyrosine kinase proposed for the treatment of adult patients with advanced or metastatic *RET* fusion positive NSCLC.

The proposed strengths are 40 mg and 80 mg. The product will be distributed in blisters containing 14, 42, 56, or 168 capsules for the 40 mg strength and 14, 28, 56 or 112 capsules for the 80 mg strength.

Figure 1: Chemical structure of selpercatinib



The Delegate noted that the foil packaging will require a Section 14 exemption at the time of Registration due to the positioning of the text for Lot and Expiry Date not being consistent with Therapeutic Goods Order 91 (TGO 91).[2] The text is, however, directly subjacent to where this information will be displayed.

The Delegate concurs with the quality evaluator's view that there is no significant safety issue raised by this minor departure from TGO91, which only occurs on the foil packaging for the capsules and not on the exterior box.

The Delegate noted that approval for registration of the proposed product can be recommended from a pharmaceutical chemistry perspective.

Nonclinical

The Delegate noted that no major nonclinical deficiencies were identified.

Primary pharmacology studies demonstrated nonclinical efficacy for the intended target of *RET*-related kinases and support the use of selpercatinib for the proposed indications.

Off-target inhibitory activity of selpercatinib was observed against a number of other kinases at clinically relevant concentrations – notably Aurora B, FGFR1, FGFR2, FGFR3, FLT1 (VEGFR1), VEGFR2, FLT4 (VEGFR3), PLK4, 5-HT and α2c(h). Pharmacological effects resulting from inhibition of these targets by selpercatinib may occur with Retevmo use.

Major targets of selpercatinib -related toxicity included:

- Lymphoid tissue (bone marrow, thymus, spleen, gut associated lymphoid tissues)
- Gastrointestinal tract
- Liver
- Bone and teeth (which may have clinical relevance to patients less than 18 years).
- Hyperphosphataemia
- Reproductive tissue

Dedicated fertility studies in male and female rats are available and were evaluated by the FDA.

[2] Therapeutic Goods Order 91 (TGO 91) describes the standards required for labels of prescription and related medicines; made under Section 10 of the Therapeutic Goods Act (1989).This Order sets out what kinds of information are required to be included on the label of prescription and other related medicines. For further information, visit the TGA website: https://www.tga.gov.au/therapeutic-goods-orders.

Clinical

The pivotal clinical data was provided by two reports of the Libretto-1 study.

A further six pharmacokinetic studies were provided and 1 pharmacodynamic study examining the effect of Selpercatinib on QTc interval.[3]

Pharmacology

Pharmacokinetics

The clinical evaluator has reviewed the pharmacokinetics (PK) data.

The general pharmacokinetic parameters of Selpercatinib are:

- A mean bioavailability of 73%, time to maximum concentration (T_{max}) of 2 hours and volume of distribution (Vd) of 323 L.
- Selpercatinib is 97% bound to plasma proteins *in vitro*, with a blood/plasma ratio of 0.7
- Selpercatinib is a mild inhibitor of CYP2C8 *in vivo* but is mainly metabolised by CYP3A4.
- Following metabolism, 69% of the dose of Selpercatinib is excreted in faeces and 24% in urine over an extended collection period in which 94% of a radio-labelled dose was recovered.

The PK studies that were submitted were:

- Study J2G-MC-JZJV examined the effect of selpercatinib on the PK of dabigatran.
- Study LOXO-RET-18014 which examined the effect of multiple doses of itraconozole and rifampicin on the PK of a single dose of selpercatinib.
- Study LOXO-RET-18017 which examined the effect of multiple doses of selpercatinib on the PK of a single dose of midazolam.
- Study LOXO-RET-18026 which examined the effect of multiple doses of selpercatinib on the PK of a single dose of repaglinide.
- Study LOXO-RE-19075 which examined the effect of multiple doses of ranitidine or omeprazole on the PK of a single dose of selpercatinib. Omeprazole was administered in periods in which the subjects were fasted, given a low-fat meal or given a high-fat meal respectively.
- Study LOXO-RET-18057 which was a dose escalation study to determine the PK of selpercatinib in healthy female subjects.

The results of these studies are, in brief:

- Coadministration of 160 mg selpercatinib with a strong CYP3A4 inhibitor (itraconazole) increased the area under concentration time curve (AUC) of selpercatinib 2.3 fold and the C_{max} 1.3 fold compared to when selpercatinib was given alone.

[3] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

- Coadministration of 160 mg selpercatinib with a strong CYP3A4 inducer (rifampicin multiple doses) decreased the AUC of selpercatinib by 87% and the maximum concentration (C_{max}) by 70% compared to when it was administered alone.
- Coadministration of 160 mg selpercatinib with a P-glycoprotein inhibitor (rifampin single dose) increased the AUC of selpercatinib by 6% and the C_{max} by 19% compared to when it was administered alone.
- Co-administration of selpercatinib under fasted conditions with omeprazole decreased the AUC of selpercatinib by 69% and C_{max} by 88% compared to when it was administered alone. When administered with a high-fat meal and omeprazole the AUC of selpercatinib was increased by 2% and the C_{max} was reduced by 49%. When administered with a low-fat meal and omeprazole the AUC of selpercatinib was unchanged, and the C_{max} was reduced by 22% compared to when administered alone.
- Coadministration of 160 mg of selpercatinib with ranitidine increased the AUC of selpercatinib by 7% and the C_{max} by 18% compared to when it was administered alone.
- Co-administration of 160 mg selpercatinib with midazolam, a CYP3A4 substrate, increased the AUC of midazolam by 1.5 fold and the C_{max} of midazolam 1.4 fold compared to when midazolam was administered alone.

Pharmacodynamics

Study LOXO-RET-18032 was a single dose study that examined the effect of selpercatinib on QTc. This suggested a mild prolongation in QTc at 320 mg and 640 mg of selpercatinib, which has been noted as a potential risk in the draft PI.

Efficacy

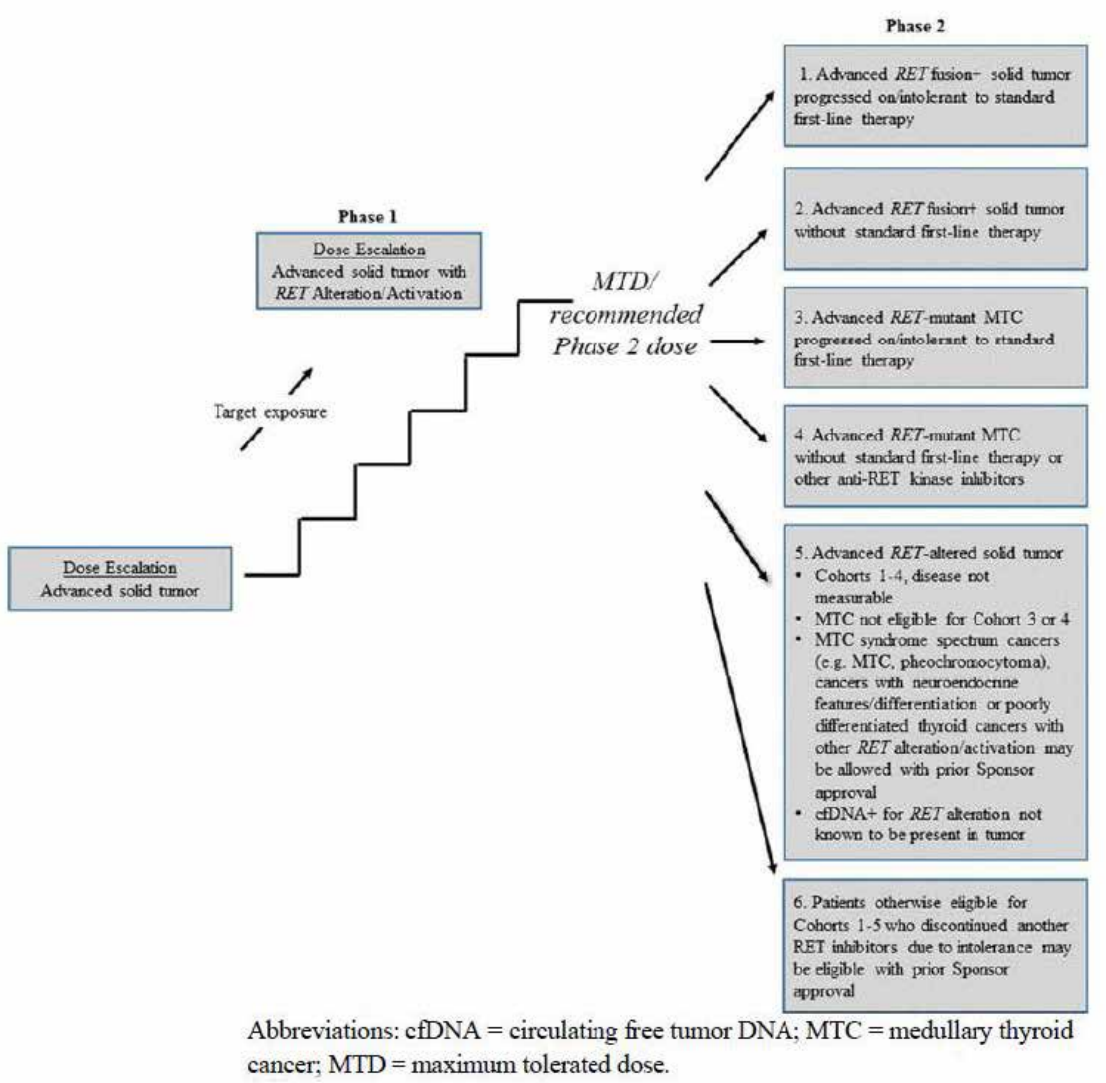
Pivotal data

Study Libretto-001 provided the pivotal data for this submission. Three data-analyses of the study were provided on15 June 2021, 17 June 2019 and 16 December 2019. Of these, the clinical evaluation report has focused on the latest data cutoff in 2021 as this provides the longest timeline for efficacy and safety analyses.

Libretto-001

Study Libretto-001 was an open label Phase I/II study of Selpercatinib in patients with advanced solid tumours, including those with RET activation.

Figure 2:Study Libretto-001 design



Abbreviations: cfDNA = circulating free tumor DNA; MTC = medullary thyroid cancer; MTD = maximum tolerated dose.

The first part of the study was a dose escalation protocol ranging from 20 mg once daily to 240 mg twice daily, after which 160 mg twice daily was selected for further study in part two. In part two subjects received selpercatinib until disease progression or discontinuation of therapy for other reasons (for example, toxicity etc).

For the analysis of the proposed indication all included patients were adults with advanced or metastatic NSCLC who had:

1. One of:

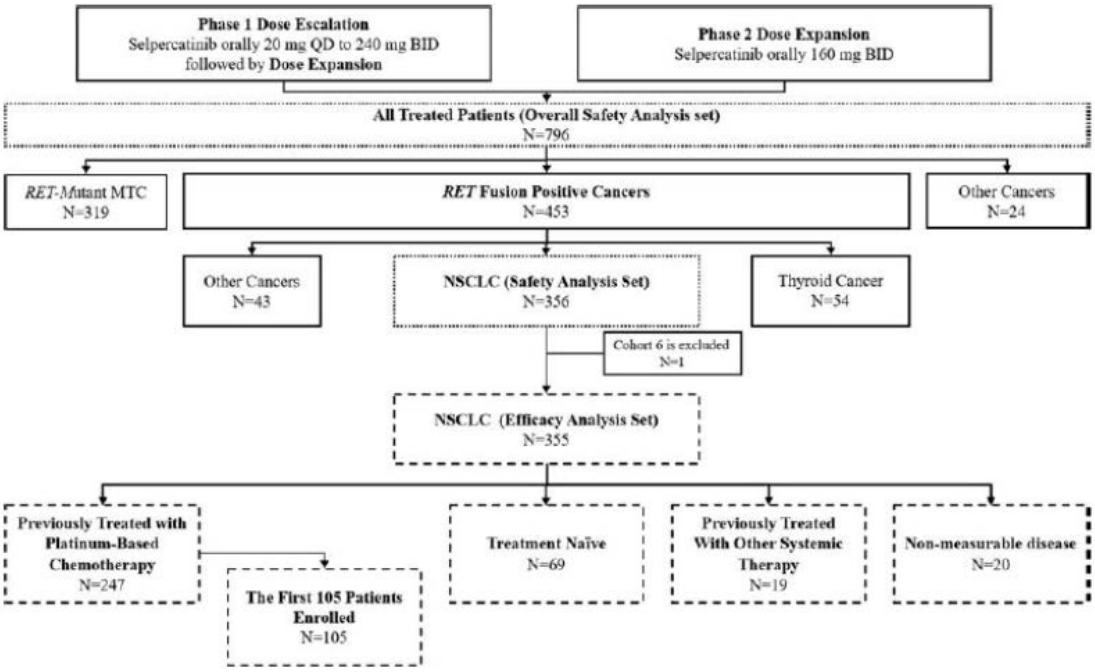
- Progressed on, or were intolerant to, standard therapy
- For whom no standard therapy exists or, in the opinion of the Investigator the subject was not a candidate for standard therapy or was unlikely to tolerate or derive benefit from standard therapy
- Declined standard therapy

2. Subjects had not received prior targeted anti-RET therapy, but were allowed to have received multi-kinase inhibitors.

3. A *RET* gene alteration

4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2;[4]
5. Life expectancy of at least 3 months.

Figure 3: Study Libretto-001 Patient disposition



Abbreviations: BID = twice daily; MTC = medullary thyroid cancer; N = number of patients; NSCLC = non-small cell lung cancer; QD = once daily; RET = REarranged during Transfection.

The overall NSCLC efficacy analysis population comprised 355 patients, although sub-analyses were performed based in prior therapy. This population had an average age of 61 years, with a slight preponderance of women (57.2%) and a majority of never-smokers (67.9%).

The majority of patients had received prior platinum based chemotherapy (n = 247), although a significant cohort were treatment naïve (n = 69). An analysis of the first 105 patients enrolled who had been treated with previous platinum based chemotherapy was also provided, giving slightly longer follow-up by the data cutoff than the general population.

[4] Eastern Cooperative Oncology Group Performance Status (ECOG PS): The ECOG has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

The primary endpoint examined in Libretto-001 was the objective response rate (ORR) based on the Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 criteria.[5]

In the 247 patients previously treated with platinum based chemotherapy, the ORR at a median follow up of 21.19 months was 61.1%.

Table 3: Study Libretto-001 Efficacy endpoints for previously treated patients (n = 247)

	IRC Assessment (N=247)	Investigator Assessment (N=247)
Objective Response Rate[a,b]		
n (%)	151 (61.1)	159 (64.4)
95% CI	(54.7, 67.2)	(58.1, 70.3)
Best Overall Response – n (%)		
Complete response (CR)	18 (7.3)	9 (3.6)
Partial response (PR)	133 (53.8)	150 (60.7)
Stable disease (SD)	81 (32.8)	74 (30.0)
SD -16 weeks[c]	60 (24.3)	55 (22.3)
Progressive disease (PD)	7 (2.8)	5 (2.0)
Not evaluable	8 (3.2)	9 (3.6)
Clinical Benefit Rate (CR + PR + SD-16 weeks[c])[d]		
n (%)	211 (85.4)	214 (86.6)
95% CI[b]	(80.4, 89.6)	(81.8, 90.6)
Duration of Response (months)[e,f]		
Median (95% CI)	28.58 (20.4, NE)	21.22 (18.4, 31.8)
Censored n (%)	92 (60.9)	80 (50.3)
Duration of Follow-Up (months)[e]		
Median	21.19	23.20
25th, 75th percentiles	16.6, 26.0	20.3, 29.5
Rate (%) of Duration of Response[e,g]		
≥6 months (95% CI)	86.9 (80.3, 91.5)	89.2 (83.2, 93.1)
≥12 months (95% CI)	73.1 (64.9, 79.7)	73.4 (65.6, 79.6)
≥24 months (95% CI)	55.8 (46.4, 64.2)	46.2 (37.3, 54.7)
≥36 months (95% CI)	49.4 (37.5, 60.3)	26.3 (12.1, 42.8)

In the 69 treatment naïve population, the ORR at a median follow up of 20.21 months was 84.1%.

This gave an overall-survival (OS) rate in these 247 patients of 87.9%, 68.9% and 58.5% a 12, 24 and 36 months respectively.

Progression-free survival (PFS) was 70.5%, 51.4% and 42.6% at 12, 24 and 36 months respectively.

[5] The Response Evaluation Criteria In Solid Tumours (RECIST) is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

Table 4: Study Libretto-001 Efficacy endpoints for treatment-naïve patients (n = 69)

	IRC Assessment (N=69)	Investigator Assessment (N=69)
Objective Response Rate[a]		
n (%)	58 (84.1)	59 (85.5)
95% CI	(73.3, 91.8)	75.0, 92.8
Best Overall Response – no. (%)		
Complete response (CR)	4 (5.8)	1 (1.4)
Partial response (PR)	54 (78.3)	58 (84.1)
Stable disease (SD)	6 (8.7)	5 (7.2)
SD≥16 weeks[c]	6 (8.7)	4 (5.8)
Progressive disease (PD)	3 (4.3)	3 (4.3)
Not evaluable	2 (2.9)	2 (2.9)
Clinical Benefit Rate (CR + PR + SD[c])[d]		
n (%)	64 (92.8)	63 (91.3)
95% CI[b]	(83.9, 97.6)	(82.0, 96.7)
Duration of Response (months)[e,f]		
Median (95% CI)	20.21 (13.0, NE)	20.27 (14.8, NE)
Censored	32 (55.2)	31 (52.5)
Duration of Follow-Up (months)[e]		
Median	20.27	23.03
25th, 75th percentiles	12.9, 26.7	15.2, 26.5
Rate (%) of Duration of Response[e,g]		
≥6 months (95% CI)	87.7 (75.9, 93.9)	86.2 (74.3, 92.9)
≥12 months (95% CI)	66.1 (51.6, 77.3)	66.3 (52.4, 77.1)
≥24 months (95% CI)	41.6 (25.6, 56.8)	41.8 (26.1, 56.7)
≥36 months (95% CI)	41.6 (25.6, 56.8)	41.8 (26.1, 56.7)

This gave an overall survival rate in these 69 patients of 92.7%, 69.3% and 57.1% at 12, 24 and 36 months respectively.

Progression free survival was 70.6%, 41.6% and 38.4% a 12, 24 and 36 months respectively.

An analysis in a small group of patients with brain metastases (n = 26) indicated relatively similar results, including for patients who had received radiotherapy (n = 10) and who had not received radiotherapy (n = 16)).

Safety

The median exposure time in the safety analyses set provided by Study Libretto-001 was 21.29 months for all patients, and 19.09 months for the NSCLC cohorts.

Table 5: Study libretto-001 Adverse events occurring in greater than 15% of patients

	Maximum Severity Patient Incidence, n (%)			
	NSCLC Safety Population (N=356)		Overall Safety Population (N=796)	
Preferred or Composite Term	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Edema	178 (50.0)	2 (0.6)	386 (48.5)	6 (0.8)
Diarrhea	184 (51.7)	15 (4.2)	374 (47.0)	40 (5.0)
Fatigue	153 (43.0)	8 (2.2)	365 (45.9)	25 (3.1)
Dry Mouth	163 (45.8)	0 (0.0)	344 (43.2)	0 (0.0)
Hypertension (AESI)	141 (39.6)	68 (19.1)	326 (41.0)	157 (19.7)
Aspartate aminotransferase increased	149 (41.9)	37 (10.4)	292 (36.7)	70 (8.8)
Alanine aminotransferase increased	147 (41.3)	53 (14.9)	284 (35.7)	91 (11.4)
Abdominal pain	101 (28.4)	5 (1.4)	268 (33.7)	20 (2.5)
Constipation	96 (27.0)	5 (1.4)	261 (32.8)	6 (0.8)
Rash	130 (36.5)	4 (1.1)	261 (32.8)	5 (0.6)
Nausea	112 (31.5)	4 (1.1)	248 (31.2)	9 (1.1)
Blood creatinine increased	92 (25.8)	10 (2.8)	227 (28.5)	15 (1.9)
Headache	94 (26.4)	3 (0.8)	220 (27.6)	11 (1.4)
Cough	87 (24.4)	0 (0.0)	184 (23.1)	0 (0.0)
Dyspnea	84 (23.6)	16 (4.5)	179 (22.5)	25 (3.1)
Vomiting	78 (21.9)	4 (1.1)	178 (22.4)	14 (1.8)
ECG QT prolongation (AESI)	74 (20.8)	21 (5.9)	168 (21.1)	38 (4.8)
Arthralgia	48 (13.5)	0 (0.0)	165 (20.7)	2 (0.3)
Back pain	65 (18.3)	3 (0.8)	153 (19.2)	12 (1.5)
Dizziness	69 (19.4)	2 (0.6)	152 (19.1)	2 (0.3)
Decrease appetite	73 (20.5)	1 (0.3)	150 (18.8)	3 (0.4)
Pyrexia	79 (22.2)	1 (0.3)	135 (17.0)	1 (0.1)
Urinary tract infection	70 (19.7)	8 (2.2)	135 (17.0)	12 (1.5)
Thrombocytopenia	74 (20.8)	20 (5.6)	123 (15.5)	24 (3.0)
Dry skin	57 (16.0)	0 (0.0)	122 (15.3)	0 (0.0)
Hypocalcaemia	21 (5.9)	3 (0.8)	121 (15.2)	22 (2.8)

The most commonly reported adverse events in patients receiving selpercatinib were dry mouth (42.4%), oedema (34.8%), AST increase (34.3%) and ALT increase (33.7%).

The incidence of treatment emergent adverse events (TEAE) of Grade three severity or higher was 40.2%. The most common of these were hypertension (13.8%), ALT increased (11.5%) and AST increased (6.7%). Pneumonia occurred in 5% of patients, pleural effusion in 3%, abdominal pain in 2.5% haemorrhage in 2.4%, dyspnoea in 2.3% and hyponatraemia on 2.3% of cases.

There were no cases of rises in transaminase that were consistent with Hy's law.

Overall, 0.6% of patients had adverse events serious enough to cause discontinuation of therapy, 8.7% leading to dose reduction and 13.2% leading to a dose being withheld.

The clinical evaluator has noted that clinical chemistry and haematology endpoints did not raise safety concerns.

The QT prolongation was monitored based on the results of Study LOXO-RET-18032. QT prolongation was noted in 20.8% of patients, of which 7.6% was Grade 1, 7.3% was Grade 2, and 5.9% was Grade 3.

Table 6: Degrees of QTc prolongation observed in patients receiving selpercatinib

	NSCLC Safety Population (N=356)	Overall Safety Population (N=796)
No. of Patients with QT Prolongation, n (%)		
Any Grade	74 (20.8)	168 (21.1)
Grade 1	27 (7.6)	66 (8.3)
Grade 2	26 (7.3)	64 (8.0)
Grade 3	21 (5.9)	38 (4.8)
Grade 4	0 (0.0)	0 (0.0)
Grade 5	0 (0.0)	0 (0.0)
Study Drug Related QT Prolongation	57 (16.0)	130 (16.3)
Serious AESI of QT Prolongation	0 (0.0)	1 (0.1)
Study Drug Related Serious AESI of QT Prolongation	0 (0.0)	0 (0.0)
Number of Subjects with		
QT Prolongation Leading to Dose Withheld	18 (5.1)	35 (4.4)
QT Prolongation Leading to Dose Reduction	12 (3.4)	25 (3.1)
QT Prolongation Leading to Drug Discontinuation	0 (0.0)	0 (0.0)
Time to First Onset of QT Prolongation (weeks)		
n	74	168
Mean (SD)	17.6 (28.07)	19.6 (31.47)
Median	4.1	4.1
Minimum, Maximum	0.1, 112.7	0.1, 139.9

Abbreviations: AESI = adverse event of special interest; N = number of patients; n = number of patients in specific category; NSCLC = non-small cell lung cancer.

Severe interstitial lung disease was noted in patients treated with selpercatinib. This occurred in 1.8% of patients, including 0.3% with Grade 3-4 events and 0.3% with fatal reactions.

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 1.1 (dated 25 October 2021; data lock point (DLP) 15 June 2021) and Australia specific annex (ASA) version 1.0 (dated June 2022) in support of this application. In response to TGA's questions, the sponsor has submitted EU-RMP version 3.2 (dated 2 November 2022; DLP 15 June 2021) and ASA version 2.0 (dated 30 January 2023) in support of its application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 7. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 7: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	ü	–	ü	–
Important potential risks	Liver injury	ü	–	ü	–
	Cardiac arrhythmia due to QT prolongation	ü	–	ü	–
	Reproductive and developmental toxicities	ü*		ü	

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Growth plate abnormalities in paediatric patients†	ü†	–	ü†	–
Missing information	Exposure and safety in patients with severe hepatic impairment	ü	–		–
	Exposure and safety in patients with cardiac impairment	ü	–	–	–

* Pregnancy and breast-feeding follow-up forms

† EU-RMP only and applicable to paediatric indications in the EU.

No new safety concerns have been identified by the clinical evaluator. The summary of safety concerns aligns with the EU-RMP (except for safety concern pertaining to the paediatric indications in the EU only) and is satisfactory

Routine pharmacovigilance activities only are proposed. Routine pharmacovigilance includes follow up forms for pregnancy and breast feeding. The sponsor has clarified that there will be standard adverse event follow up forms titled 'hepatic disorders' and 'cardiac disorders' as 'liver injury' and 'cardiac arrhythmia due to QT prolongation' are surveillance terms for selpercatinib. The pharmacovigilance plan is acceptable.

The sponsor has provided a clinical study plan for the provisional application. This will be reviewed by the Delegate for adequacy.

Routine risk minimisation activities only are proposed. This is acceptable as selpercatinib is an oral medication which will be prescribed by specialist physicians and no additional educational materials are required.

Risk-benefit analysis

Delegate's considerations

Non-small cell lung cancer is a highly aggressive tumour for which the identification of targetable mutations has been shown to improve clinical response compared to non-specific chemotherapy. Although Study Libretto-001 is not a controlled trial, the natural history of advanced or metastatic NSCLC is sufficiently well understood to offer a comparison. On this basis, the Delegate is of the view that selpercatinib provides a potential benefit over response rates to platinum based chemotherapy. This is caveated by the relatively short period of follow up in Study Libretto-001, and early responses to therapy may not be sustained.

Selpercatinib appears well tolerated within the context of systemic therapies for NSCLC. The US FDA has added additional adverse events to the product labelling during its evaluation of this indication, and these have been included in the updated Australian PI. However, the Delegate notes that the lack of comparative safety data for this product, and the relative recency of its introduction into clinical practice, poses a risk that adverse events will emerging that are not reported in the current trial data.

The Delegate considers the main issue with the data provided to be the clinical population for whom the results are most relevant.

The majority of subjects in Study Libretto-001 had received prior chemotherapy and had a three month life-expectancy at enrolment. This may suggest a second-line indication is appropriate, and the European Medicines Agency intially registered selpercatinib for patients who have

received prior platinum based chemotherapy. It has subsequently moved to an indication for all *RET*-positive tumors not previously treated with a *RET* inhibitor.

However the response to therapy in Study Libretto-001 was similar in most metrics between pre-treated treatment-naïve patients. The Delegate notes that the inclusion of treatment-naïve patients on the basis of non-specified investigator or patient preference against 'standard therapy' may have introduced a selection bias to these results. However, the Delegate feels that this is unlikely to invalidate the observation that selpercatinib was effective in a small cohort of first-line patients. The US FDA has approved selpercatinib for a line-agnostic indication to treat NSCLC.

Proposed action

The Delegate is currently minded to approve the Provisional Registration of Selpercatinib '*for the treatment of adult patients with advanced metastatic RET fusion positive non-small cell lung cancer (NSCLC)*'.

For clarity, the Delegate will consider the advice of the Advisory Committee on Medicines (ACM) regarding the indication for selpercatinib to be determinative in the final decision.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***The advice of the ACM is sough as to whether selpercatinib should be provisionally registered for all RET-positive NSCLC or only those in whom systemic therapy is required after receiving platinum-based chemotherapy.***

The ACM advised that the efficacy and safety data available at this time supported provisional registration of selpercatinib for *RET*-positive NSCLC.

The ACM did not support limiting the indication to a second or later line of treatment. The inclusion criteria of the pivotal study did not require prior platinum-based chemotherapy. The objective response rate at a median follow-up of 20.21 months was 84.1% in treatment-naïve patients (n = 69) compared to an objective response rate at a median follow-up of 21.19 months of 61.1% in patients previously treated with platinum based chemotherapy (n = 247).

The ACM discussed whether the wording of the proposed indication of 'advanced and metastatic' excluded 'locally advanced' disease, noting that locally advanced disease (Stage IIIA and IIIB) may not be curable by surgery or chemoradiation. The ACM referred to the Study Libretto-001 inclusion criterion of '*patients with a locally advanced or metastatic solid tumour*'. In the Australian context, an indication for advanced or metastatic disease when surgery is not indicated would broadly reflect the criteria of the pivotal study and allow clinicians to select appropriate patients for this medicine. The ACM also discussed the use of metastatic and advanced within the indication wording and noted that advanced and metastatic are not the same, however advanced often includes cases of metastatic disease. The ACM reiterated that the indication wording should align with the clinical trials and not infer use in the adjuvant or neoadjuvant setting however should also allow for clinician expertise and judgement to be exercised.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Retevmo has provisional approval for the treatment of adult patients with advanced or metastatic RET fusion positive non-small cell lung cancer (NSCLC) when surgery is not indicated.*
>
> *The decision to approve this indication has been made on the basis of objective response rate (ORR) and duration of response (DOR) from a single arm study. Continued approval of this indication depends on verification and description of benefit in a confirmatory trial.*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Retevmo (selpercatinib) 40 mg, 80 mg, immediate released hard capsule, blister pack, indicated for:

> *Retevmo has provisional approval for the treatment of adult patients with locally advanced or metastatic RET fusion positive non-small cell lung cancer (NSCLC).*
>
> *The decision to approve this indication has been made on the basis of objective response rate (ORR) and duration of response (DOR) from a single arm study. Continued approval of this indication depends on verification and description of benefit in a confirmatory trial.*

Specific conditions of registration applying to these goods

- Retevmo (selpercatinib) is to be included in the Black Triangle Scheme. The PI and CMI for Retevmo must include the black triangle symbol and mandatory accompanying text for five years, or the product's entire period of provisional registration, whichever is longer.
- The Retevmo EU-RMP (version 3.2, dated 2 November 2022, DLP 15 June 2021), with ASA (version 2.0, dated 30 January 2023), included with Submission PM-2022-02343-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- Specifically, the sponsor must conduct studies as described in the clinical study plan in version 2.0 (dated 30 January 2023) of the ASA. The following study report(s) should be submitted to the TGA:

- Study J2G-OX-JZJA (LIBRETTO-001) by 2024
- Study J2G-MCJZJC (LIBRETTO-431) by 2026

Attachment 1. Product Information

The PI for Retevmo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

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Reference/Publication #